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Uveitis associated with cancer immunotherapy: long-term outcomes

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1 Title page

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3 Uveitis associated with cancer immunotherapy: long-term outcomes

4

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20

21

22 Abbreviated title: Cancer immunotherapy-associated uveitis

23

24 **Key words**

25 Uveitis, macular edema, hypopion, cancer immunotherapy, rituximab, nivolumab,
26 ipilimumab, anti-BRAF, anti-MEK, ibritunib

27

28 **Abstract**

29 Background : to report the long-term outcome of uveitis associated with cancer
30 immunotherapy (CIT)

31 *Methods:* retrospective review of serial patients with CIT-associated uveitis treated using
32 various regimen.

33 *Results:* Eight included patients treated with rituximab (anti-CD20), nivolumab (anti-PD-1),
34 ipilimumab (anti-CTLA-4), vemurafenib and dabrafenib (anti-BRAF), trametinib (anti-MEK),
35 and ibritunib, showed uveitis with hypopion (1 patient), macular edema (5 patients) and
36 choroiditis (2 patients). Various regimen of corticosteroid therapy showed a favorable
37 ophthalmological outcome, whether the CIT was continuing or suspended.

38 Discussion-Conclusion: Local corticosteroids injections in combination with CIT could be
39 suggested as a first-line treatment. This could help to preserve the quality of life without
40 threatening the vital prognosis.

41

42 **LayAbstract:**

43

44 *Purpose:*To report the long-term outcome of intra-ocular inflammation (uveitis) associated
45 with cancer immunotherapy (CIT)

46 *Methods:* Serial patients complaining of blurred vision and painful eyes, showed intra-ocular
47 inflammation that was related to CIT, after infectious, inflammatory, and tumoral causes of
48 uveitis have been ruled out. The length of follow-up was more than 12 months for most
49 patients.

50 *Results:* Eight serial patients treated with rituximab (anti-CD20), nivolumab (anti-PD-1),
51 ipilimumab (anti-CTLA-4), vemurafenib and dabrafenib (anti-BRAF), trametinib (anti-MEK),
52 and ibritunib, showed intra-ocular inflammation with hypopion (1 patient), macular edema (5
53 patients) and choroiditis (2 patients). Various regimen of corticosteroid therapy showed a
54 favorable ophthalmological outcome, whether the CIT was continuing or suspended.

55 *Conclusions:* Local corticosteroids injections in combination with CIT could be suggested as
56 a first-line treatment. This could help to preserve the quality of life without threatening the
57 vital prognosis.

58 **Key words**

59 Uveitis, macular edema, hypopion, cancer immunotherapy, rituximab, nivolumab,
60 ipilimumab, anti-BRAF, anti-MEK, ibritunib

61 **Summary points :**

- 63 1. This study reported 8 cases of CIT-associated uveitis, among which 7 experienced a visual
64 loss and 5 had a macular edema, 2 had nodular choroiditis, 1 had hypopion.
- 65 2. Changes in macular edema, choroiditis, and hypopion were analysed for a long-term
66 follow-up superior to 12 months.
- 67 3. The underlying metastatic cancer were heterogenous, and immunotherapy drugs were
68 numerous. However the clinical ophthalmological uveitis related to CIT showed a similar
69 good response to the corticosteroid treatment, regardless of further CIT.
- 70 4. At 3 months, the short-term visual outcomes were favorable after treatment with systemic
71 or local injections of cortosteroids, whether the CIT was continuing or suspended.
- 72 5. At 12 months, CIT continuation was associated with uveitis activity, that showed sustained
73 good response to sub-Tenon's triamcinolone injections.
- 74 6. So the role of the ophthalmologist may be useful in (1) making quickly the diagnosis
75 relating uveitis to CIT, ruling out infectious, auto-immune and tumoral causes (2) explaining
76 the often favorable uveitis outcome using corticosteroid local injections (3) reassuring
77 patients and oncologists, worried about visual fonction (4) performing quickly
78 ophthalmological treatment to keep a good quality of life (5) following the patients to assess
79 positive and negative treatment effects (6) repeating the corticosteroid local injections if
80 needed (7) rediscussing the treatment in case of ophthalmological failure.

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90 Uveitis associated with cancer immunotherapy: long-term outcomes

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103 PMID: 34709074 DOI: [10.2217/imt-2021-0032](https://doi.org/10.2217/imt-2021-0032)

104 Abstract

105 **Background:** We report the long-term outcome of uveitis associated with cancer
106 immunotherapy (CIT). **Methods:** This retrospective review included serial patients with CIT-
107 associated uveitis treated using various regimen. **Results:** Eight patients treated with
108 rituximab (anti-CD20), nivolumab (anti-PD-1), ipilimumab (anti-CTLA-4), vemurafenib and
109 dabrafenib (anti-BRAF), trametinib (anti-MEK) and ibritunib showed uveitis with hypopion
110 (one patient), macular edema (five patients) and choroiditis (two patients). Various regimens
111 of corticosteroid therapy showed a favorable ophthalmological outcome, whether the CIT was
112 continuing or suspended. **Conclusion:** Local corticosteroid injections in combination with
113 CIT could be suggested as a first-line treatment. This could help to preserve the quality of life
114 without threatening the vital prognosis.

115 **Keywords:** anti-BRAF; anti-MEK; cancer immunotherapy; hypopion; ibritunib; ipilimumab;
116 macular edema; nivolumab; rituximab; uveitis.

117 Plain Language Summary

118 Lay abstract This study aims to report the long-term outcome of intra-ocular inflammation (uveitis)
119 associated with cancer immunotherapy (CIT). Serial patients complaining of blurred vision and painful
120 eyes showed intra-ocular inflammation that was related to CIT, after infectious, inflammatory and
121 tumoral causes of uveitis have been ruled out. The length of follow-up was more than 12 months for
122 most patients. Eight serial patients treated with rituximab (anti-CD20), nivolumab (anti-PD-1),
123 ipilimumab (anti-CTLA-4), vemurafenib and dabrafenib (anti-BRAF), trametinib (anti-MEK) and ibritunib
124 showed intra-ocular inflammation with hypopion (one patient), macular edema (five patients) and
125 choroiditis (two patients). Various regimens of corticosteroid therapy showed a favorable
126 ophthalmological outcome, whether the CIT was continuing or suspended. Local corticosteroid
127 injections in combination with CIT could be suggested as a first-line treatment. This could help to
128 preserve the quality of life without threatening the vital prognosis

129 **Introduction**

130 Uveitis can affect all layers of the eye and may be due to various etiologies: autoimmune,
131 infectious, iatrogenic or tumor such as masquerade syndrome. Macular edema is the leading
132 cause of visual loss in uveitis [1,2]. Recently, a new iatrogenic uveitis entity has been
133 associated with cancer immunotherapy (CIT). CIT inhibits T-cell inactivation driven by tumor
134 cells [3,4]. The promising results of CIT have led to an increasing number of indications
135 involving larger cohorts of patients [5]. For 10 years, about 50 novel agents have been
136 approved for the treatment of metastatic cancers, including (1) monoclonal antibodies directed
137 against tumor cell surface receptors (such as rituximab, an anti-CD20); (2) immune
138 checkpoint inhibitors (ICIs) such as anti-PD-1 (pembrolizumab, nivolumab), anti-PD-L1
139 (atezolimab, avelumimab) and anti-CTLA-4 (ipilimumab) monoclonal antibodies that block
140 the interaction between inhibitory T-cell receptors and their ligands; and (3) small-molecule
141 kinase inhibitors, in particular BRAF inhibitors (vemurafenib, dabrafenib) and MEK
142 inhibitors (trametinib) that inhibit the mitogen-activated protein kinase signaling pathway
143 involved in cell regulation.

144 Immune-related adverse events (irAEs) have been associated with ICIs, BRAF inhibitors and
145 MEK inhibitors in about 25% of patients, including skin (vitiligo, rash, pruritis) and liver
146 (auto-immune hepatitis) AEs as well as colitis and thyroiditis [6,7]. However, the severity of
147 the reported ocular AEs varies from mild (dry eyes and conjunctivitis) to serious (intraocular
148 and orbital inflammation).

149 Intraocular inflammation was mainly reported in the anterior chamber while a posterior
150 segment involvement may lead to Vogt-Koyanagi-Harada (VKH) disease, retinal vascular
151 occlusion, macular edema and papillitis [8-19].

152 The aim of this study was to report the long-term outcomes of patients with CIT-associated
153 uveitis, and discuss the various therapeutic options based on a literature review.

154
155 **Patients and methods**

156 Serial patients with CIT-associated intraocular inflammation seen between January 1, 2018
157 and December 31, 2019 were retrospectively included. Patients treated with CIT and reporting
158 eye problems were promptly referred to an ophthalmologist and then to a reference tertiary
159 uveitis center. A collegial therapeutic discussion about the therapeutic interventions involving
160 oncologists, and ophthalmologists was held in a multidisciplinary meeting.

161 This was a retrospective interventional case series on the approved indications of CIT in
162 France. Informed consent was obtained for all patients before performing retinal angiography,
163 aqueous humor sampling, and before treatment change. Ethic institutional committee approval
164 was obtained.

165 For each patient, the following data were collected: cancer history and disease progression,
166 previous and current treatments, and detailed ophthalmologic examinations performed at
167 baseline and during the follow-up.

168 All subjects underwent a comprehensive eye examination including the best-corrected visual
169 acuity (BCVA) on a decimal scale converted into LogMAR, a slit-lamp examination, and a
170 dilated fundus examination. Intraocular inflammation in the aqueous humor and vitreous was
171 scored using the SUN grading system[20]. Color fundus photographs, autofluorescence
172 photographs, fluorescein (FA) and indocyanine green (ICGA) angiography were performed
173 using CR2 plus (Canon, Tokyo, Japan) devices, the HRA2 (Heidelberg Engineering,
174 Heidelberg, Germany), and Optos (Optos Inc. Marlborough, MA 01752 USA) respectively.
175 Spectral-Domain Optical Coherence Tomography (SD-OCT) was performed using the
176 Spectralis (Heidelberg Engineering, Heidelberg, Germany). Flare measurements were
177 performed using the FC-2000® flare meter (KOWA, Tokyo, Japan), to objectively quantify
178 the inflammatory reaction in the aqueous humor [21]. Goldmann visual field examinations

179 were performed by orthoptists. A thorough work-up was performed to exclude infectious and
180 common ocular and systemic auto-immune causes of uveitis. Particular attention was paid to
181 the systemic causes such as sarcoidosis that can be induced by CIT [22]. So the work-up
182 included for all patients serogy for Human Immunodeficiency virus, syphilis, Lyme disease, B
183 and C hepatitis, and Quantiferon® test, along with blood count, ionogram, protein
184 electrophoresis, sedimentation rate, angiotensine convertase enzyme, lysozyme, antinuclear
185 and anti DNA. In case of clinical doubt aqueous humor sampling was performed for
186 IL10/IL6 rate to rule out intraocular lymphoma diagnosis. HLA A29 was tested to rule out
187 Birdshot retinochoroiditis which is an auto-immune posterior uveitis characterized by fundus
188 showing deep cream-coloured spots predominantly located in nasal inferior to the optic nerve
189 head. Chest scan and brain magnetic resonance imaging results were known thanks to the
190 patient's oncologic department. If induced-sarcoidosis was suspected, pulmonary function
191 tests and salivary glandular biopsy were performed. Alternative causes of autoimmune-
192 associated or infectious uveitis were excluded from the analysis.

193
194 AE severity was graded according to the Common Terminology Criteria for Adverse Events
195 (CTCAE) version 5.0 [23].

196 The tumor response to CIT was classified according to the revised RECIST guideline [24].

197 AEs were reported to the National and world Global pharmacovigilance after checking
198 accurately each case.

199 Clinical uveitis features along with OCT, FA, ICGA, and flare meter results were described at
200 baseline and during the follow-up.

201 Therapeutic interventions were collegially discussed and decided by consensus with the
202 oncologists. They included ICI discontinuation or continuation, ICI resumption or not if ICI
203 had been previously discontinued and/or the use of systemic or local corticosteroids. Local
204 corticosteroids were given as drops or subconjunctival dexamethasone injections. Delayed
205 local corticosteroids were given as sub-Tenon's triamcilonone injections. Systemic
206 corticosteroids were given as methylprednisone pulses for 3 days followed by oral prednisone
207 at 1mg/kg for 10 days and then tapered until a daily dose of 10 mg/kg.

208 Patients were followed one month after the first examination and at least quarterly thereafter
209 to assess the efficacy of the therapeutic intervention and the occurrence of AEs. The study
210 was conducted in compliance with the Good Clinical Practice and the tenets of the
211 Declaration of Helsinki. We focussed on chronic intraocular inflammation that is a rare irAEs.
212 However, this study gave us the opportunity to discuss the risk/benefit ratio in a context of
213 life-threatening disease.

214 **Statistical analysis.**

215 Descriptive statistical analysis was performed using STATA/SE 11.0 software (College
216 Station, Texas, US). Variables were compared using a U Mann-Whitney non-parametric test
217 for continuous variables and a p-value <0.05 was considered significant.

218

219 **Results**

220 Eight patients (4 women and 4 men) with intraocular inflammation associated with CIT given
221 for metastatic cancer were included (table 1). Patients median age was 68.5 years (IQ1 60.5,
222 IQ3 75.7; range: 58-83). The presence of neoplasia and its grading are described in table 1.

223 Treatments included rituximab (case 1), ibrutinib (case 2), nivolumab (cases 4, 5, 6, 8),
224 ipilimumab (case 8), dabrafenib + trametinib (case 3), and verumafenib (case 7). One patient
225 (case 3) received a combination of nivolumab, dabrafenib and trametinib for 6 months and
226 only dabrafenib and trametinib thereafter (table 1).

227

228 Three patients experienced additional extra-ocular irAEs, including interstitial pneumonitis
229 (cases 3, 6), cryoglobulinemia (case 3), and peripheral neuropathy (case 7) leading to CIT
230 discontinuation (table 1).

231 Uveitis occurred after a median treatment duration of 4.5 months (IQ1 3.7, IQ4 14.2; range: 1-
232 24 months). Upon admission, uveitis was predominant in the anterior segment in 3 patients
233 (cases 5, 7, 8), including in association with hypopyon in 1 case (figure 5), in the intermediate
234 segment in 2 patients (cases 1, 3) and 3 patients (cases 2, 4, 6) had panuveitis. The baseline
235 features and grading of uveitis are shown in table 2. None of the patients had a previous
236 history of uveitis.

237 The median baseline VA was 0.2 LogMAR (range: 0-2) in both eyes. One patient (case 1)
238 with a history of corneal scars was monophthalmic. The median flare was 26.2 photons/ms
239 (range: 7.9-315.3) in both eyes. The median intraocular pressure was 15 mmHg (range: 9-18).
240 Posterior synechias were present in 6 eyes of 4 patients (table 2).

241 Macular edema was present in 9 eyes of 5 patients, and 3 of these patients showed macular
242 cysts that were mainly located in the inner nuclear layer (cases 2, 3, 4, figure 3). The median
243 central foveal thickness was 260 microns (range: 248-500) in both eyes. Choroidal nodular
244 lesions were seen in 4 eyes of 2 patients (cases 2, 4); on ICGA, they appeared hypofluorescent
245 10 minutes after dye injection and disappeared after 30 minutes, suggesting a stronger
246 inflammatory choroidal involvement than suggested on the fundus examination (Figure 4).

247 No case of diplopia and ocular paralysis was found. No systemic auto-immune disease
248 induced by CIT was found; in particular the sarcoidosis work-up was negative.

249 The first-line therapeutic intervention was based on corticosteroids. Systemic corticosteroids
250 were given in 2 patients with a good ophthalmological response at 3 months in both cases
251 (case 2 and case 6, respectively). Corticosteroids were injected locally in 4 patients with a
252 good ophthalmological response at 3 months. CIT was discontinued in 4 patients: 2 due to
253 ocular AEs (cases 1, 5) and 2 due to extra-ocular AEs (cases 6, 7) (Table 1).

254 At 3 months, the median BCVA was 0.05 LogMAR (range: 0-2) in both eyes and was
255 significantly different compared to the mean baseline VA ($p = 0.02$). The median flare ($n=5$)
256 was 8.0 photons/ms (IQ1 3.1, IQ4 19.6; range: 2.1-54.3) in both eyes and was significantly
257 different compared to the baseline value ($p = 0.001$). The median central foveal thickness was
258 273 microns (IQ1 264, IQ4 366; range: 231-376) in both eyes and was significantly different
259 compared to the baseline value ($p < 0.001$).

260
261 The second-line therapeutic intervention consisted in CIT resumption at various timepoints:
262 (1) at 1 month, with a switch from vemurafenib to nivolumab in 1 patient (case 7), and from
263 ipilimumab to nivolumab in 1 patient (case 8); (2) at 6 months in 1 patient (case 5), associated
264 with an increase in tumor mass leading to a rapid death; and (3) at 3 years in 1 patient (case 1)
265 without uveitis recurrence in the short term.

266 Meanwhile, CIT was continued in 3 patients (cases 2, 3, 4) and did not seem to prevent a good
267 ophthalmological response at 3 months in these three cases. However, bilateral uveitis
268 remained active in 2 out of these 3 patients (cases 3, 4). Case 3 presented a good response to
269 sub-Tenon's triamcilonone injections with a sustained efficiency on the macular edema. Case
270 4 experienced a recurrence of bilateral uveitic macular edema, but unfortunately the patient
271 died before receiving a new ophthalmological intervention.

272

273 **Discussion**

274 This study reported 8 cases of CIT-associated uveitis, among which 7 experienced a visual
275 loss. Five had a macular edema, 2 had nodular choroiditis, and 1 had hypopyon. The follow-up
276 was at least 12 months, except for the last included patient case 8. So changes in ME,
277 choroiditis, and hypopyon had been analysed for a long-term period of time. First, at 3

278 months, the short-term visual outcomes were favorable after corticosteroids treatment using
279 either systemic or local injections way. CIT was continued in 3 patients, with no negative
280 effects on the ophthalmological response. At 12 months, CIT continuation was associated
281 with sustained uveitis activity in 2 patients: one died a few weeks later and the other one
282 received sub-Tenon's triamcinolone injections every 10 months.

283 The occurrence of CIT uveitis has been currently described in metastatic melanomas (4/8
284 patients) as in other advanced cancers, suggesting that the uveitis is associated with the CIT
285 rather than related to the immune response to the original cancer. Moreover the visual fields
286 of the current patients were preserved contrary to what is usually found in cancer associated
287 retinopathy and melanoma associated retinopathy which are subtypes of paraneoplastic
288 syndrome. Two current patients were investigated for antigenic retinal proteins known to be
289 remated to cancer-associated retinopathy, in particular arrestin and recoverin search was
290 negative.

291
292 The reported incidence of severe ocular irAEs is less than 1% [16,25]. A prevalence and an
293 incidence of irAEs of respectively 0.4% and 0.7 per 1,000 patients-months have been reported
294 in patients treated with anti-PD-L1 [10]. Another recent systematic review on the ocular
295 manifestations associated with ICIs has reported an estimated prevalence ranging between
296 0.3% and 0.6% [13].

297 Combining nivolumab and ipilimumab has been associated with a stronger antitumor effect,
298 but also with more irAEs, such as uveitis, with a frequency of 6% [26-28]. In a systematic
299 review of 234 patients, ipilimumab has also been strongly associated with irAEs, including
300 autoimmune complications in 10.3% of cases, 4.3% being classified as uveitis [29].

301 In a review on ocular toxicities induced by targeted anticancer agents, Fu et al. have found
302 that small-molecule drugs are associated with a higher incidence of ocular toxicities than
303 monoclonal antibodies (37.5% *versus* 28.6%) [30].

304
305 A mean age of 54 ± 10 years has been reported at the time of the diagnosis of uveitis in
306 patients treated with anti-CTLA-4 and anti-PD-1 antibodies (ipilimumab/pembrolizumab,
307 nivolumab/acetoluzumab, avelumab, durvalumab) [31]. In the current study the patients were
308 younger and this could be due to the various types of neoplasia included.

309
310 Uveitis occurred after a median treatment duration of 4.5 months, close to previously described
311 treatment durations. Indeed, in a review of 15 cases of uveitis associated with anti-CTLA-4
312 and anti-PD-1 antibodies, most cases occurred in the first 6 months following ICI initiation
313 [31]. However, shorter treatment durations have also been associated with the occurrence of
314 uveitis. In patients treated with nivolumab and pembrolizumab, 15 cases of uveitis have been
315 reported by Wei Wang et al. after a median treatment duration of 9 weeks [32]. After an
316 infusion of anti-PD-1 and anti-PD-L1 antibodies, the median period of time to ocular irAE
317 occurrence was 29 ± 41 days [10]. In our study, uveitis also occurred after treatment
318 discontinuation in one patient as previously described [10].

319
320 The CIT-associated uveitis is usually bilateral; no strictly unilateral cases have been reported.
321 They corresponded either to enucleated patients or corneal scars preventing the intraocular
322 evaluation, as for one patient of the current study [8,33].

323
324 The spectrum of CIT-associated uveitis ranged from anterior uveitis to panuveitis. Most of the
325 reported cases had anterior uveitis, as in the case series of 22 CIT-associated uveitis reported
326 by Whilst et al. in which half of the patients had anterior uveitis [8,16,34-40]. Posterior
327 segment inflammation showed various aspects, and most of them are summarized in table 3

328 [41-59]. Serous retinal detachment suggesting VKH-like disease has been reported with the
329 use of anti-CTLA-4 treatment [41,42] and nivolumab combined with antiBRAF [11,46].
330 Moreover, bilateral cystoid macular edema shown in 4 of the current cases has been
331 previously reported to be associated with nivolumab [14,15,45], BRAF [12,52] and MEK
332 inhibitors [8,53]. The cysts were mainly located in the inner nuclear layer in 3 out of the 4
333 current cases experiencing cystoid macular edema (cases 1, 3, 4), as previously shown in a
334 large case series [8]. The inner and outer layers were more rarely involved (case 1) [45]. ME
335 has been previously reported in patients treated with rituximab [57-59].

336 An association between ibrutinib, Bruton tyrosine kinase inhibitor, and macular edema has
337 been previously reported [56]. In the global pharmacovigilance database (Vigilyze), 46 cases
338 of uveitis associated with ibrutinib (3 in France) have been reported, and ibrutinib was the
339 only suspected drug in 44 cases. The disproportionality analysis (based on the IC025) was
340 significant, suggesting an over-representation of AEs compared to other drugs.

341
342 Optic disc edema, papillitis, and leakage of the optic nerve head have been reported, in
343 particular in patients treated with pembrolizumab [34], in patients with severe hypotony
344 treated with pembrolizumab [50], and in patients treated with nivolumab [15]. Choroidal
345 involvements seen as hypofluorescent spots on ICGA were found in 2 current patients and
346 previously reported in patients treated with ipilimumab, nivolumab and pembrolizumab
347 [16,43,44,47].

348
349 In a recent study of 22 cases of CIT-associated uveitis, the combination of trametinib and
350 dabrafenib has been most often associated with the occurrence of inflammatory macular
351 edema [8]. Among the ICIs, nivolumab has been associated with posterior pole inflammation
352 leading to macular edema or disc leakage, and peripheral leakage on FA [15,31,43,45].
353 Pembrolizumab has also been associated with macular edema and disc and peripheral leakage
354 [33,48].

355 In patients treated with anti-CTLA-4 antibodies, including ipilimumab and tremelimumab,
356 secondary uveitis has been frequently reported. Anti-CTLA-4 antibodies act on the lymph
357 nodes while anti-PD-1 antibodies act in the peripheral tissues [60]. This could explain why
358 CTLA-4-associated irAEs are more common than anti-PD-1/anti-PD-L1-associated irAEs
359 [61].

360
361 Uveitis was scored using the CTCAE version 5.0 that defines successive grades [23]. Grade 1
362 corresponds to anterior uveitis with trace cells, grade 2 to anterior uveitis with 1 to 2+ cells,
363 grade 3 to anterior uveitis with 3+ or more cells or intermediate/posterior/panuveitis and
364 grade 4 to a vision at 20/200 or worse in the affected eye. Thresholds at which treatment
365 should be discontinued have been defined based on irAE severity. In particular, ICI
366 discontinuation in the presence of any grade 3 or 4 irAE has been suggested, associated or not
367 with the use of systemic corticosteroids [61]. However, the application of the CTCAE grading
368 scale may be limited to ocular toxicity management. In our series, even grade 3 and 4 irAEs
369 responded well to dexamethasone subconjunctival injections, long-term dexamethasone
370 drops, and sub-Tenon's triamcinolone injections, avoiding the initiation of systemic
371 corticosteroids. Previous studies have described a good response to local corticosteroid
372 injections. For example, grade 4 panuveitis with bilateral serous retinal detachment in patients
373 treated with nivolumab has been successfully treated with late dexamethasone implant
374 injections (Ozurdex®) [32]. Recent studies have shown a similar successful control of
375 inflammation using local corticosteroid injections and drops in patients treated with ICs,
376 associated with targeted therapy [10,19].

377 Overall, a high sensitivity to corticosteroids has been observed in cases of anterior uveitis and
378 most cases of posterior uveitis and panuveitis reported associated with CIT [8,10,19].

379
380 The AEs of local corticosteroid injections are well known and include induced cataract and
381 glaucoma. For example, cataract occurrence has been reported at 6 months in 20% of uveitis
382 eyes treated by corticosteroid periocular injections [62]. However, cataract surgery is a well
383 codified procedure, especially in elderly patients. Moreover, the endophthalmitis rate has been
384 reduced using systematic intracameral cefuroxime injections at the end of the surgical
385 procedure [63]. That is why cataract may appear as an acceptable AE in elderly patients
386 undergoing surgery with a rapid visual improvement.

387 Regarding raised intraocular pressure, it reached ≥ 24 mmHg in one third of eyes 6 months
388 after periocular corticosteroid injections in patients treated for uveitis [62]. Thus, the
389 intraocular pressure should be monitored in the second month following local corticosteroid
390 injections.

391
392 **Systemic corticosteroids:** The efficacy of systemic corticosteroids has been reported in
393 uveitis secondary to CIT in various case reports, as in 2 of the current patients [11,41,
394 44,46,48,49]. Indeed, the classical management of macular edema associated with bilateral
395 uveitis may include systemic corticosteroids as a first-line therapy, associated with
396 immunosuppressive and immunomodulatory agents thereafter to spare the daily corticosteroid
397 dose needed to control uveitis, and a treatment algorithm has been previously suggested
398 [64,65]. However, it has been suggested that systemic corticosteroids could decrease the
399 overall response in patients treated with anti-PD-(L)1 antibodies for lung cancer and taking
400 more than 10 mg/kg of prednisone daily [66]. On the other hand, systemic corticosteroids
401 have been shown not to influence the antitumor response to anti-CTL-4 [67].

402
403 **CIT discontinuation:** In a recent study, ICIs were continued in 2 patients despite the
404 occurrence of ocular complications and their ocular irAEs were resolved at 1 and 6 months,
405 respectively [10]. In our series, CIT discontinuation for 6 months was associated with tumor
406 progression and a rapid death despite a late resumption in one patient.

407 Thus, CIT continuation while promptly managing uveitis with corticosteroids injections could
408 be discussed as a first-line therapy.

409
410 **Recurrence of uveitis:** A tendency to relapse was observed in 2 of our patients after CIT
411 restart, as previously reported in studies assessing various ICIs, in particular nivolumab,
412 pembrolizumab, and ipilimumab [8,19,32]. In case of posterior pole involvement,
413 corticosteroid injections could be repeated if well tolerated. Moreover, the long-term use of
414 dexamethasone drops has been suggested to effectively maintain a low level of inflammation
415 in the anterior chamber [19].

416
417 All previous recommendations suggest to have an immediate assessment performed by an
418 ophthalmologist in case of ophthalmological problem [61,68].

419 In the context of a first-line management, it could be justified to use first topical and peri-
420 ocular injections of corticosteroids while continuing CIT. Most of the current cases were good
421 responders to local corticosteroids, even patients with a severe vision loss, and patients with
422 inflammation of the macular area.

423 The use of corticosteroids as a first line is supported by: (1) the good response to
424 corticosteroids of the inflammation in the aqueous humor and the posterior pole, (2) the long
425 period of time to recurrence, (3) the advanced age of patients making acceptable the
426 occurrence of cataract as an AE, and (4) the possibility to avoid the use of systemic

427 corticosteroids that could negatively affect the expected response. Moreover, CIT
428 continuation did not seem to prevent a good visual prognosis. CIT discontinuation should be
429 discussed on a case-by-case basis, in case of poor response to the ophthalmological treatment.
430 Although the underlying metastatic cancer are heterogenous, and immunotherapy drugs are
431 numerous, the clinical ophthalmological uveitis related to CIT had shown a similar response
432 to the corticosteroid treatment, regardless of further CIT. So the role of the ophthalmologist
433 may be useful in (1) making quickly the diagnosis relating uveitis to CIT, ruling out
434 infectious, auto-immune and tumoral causes (2) explaining the often favorable uveitis
435 outcome using corticosteroid local injections (3) reassuring patients and oncologists, worried
436 about visual fonction (4) performing quickly ophthalmological treatment to keep a good
437 quality of life (5) following the patients to assess positive and negative treatment effects (6)
438 repeating the corticosteroid local injections if needed (7) rediscussing the treatment in case of
439 ophthalmological failure.

440
441 **This study has some limitations**, including the lack of power due to a small sample size.
442 Moreover, this was a real-life study in which various types of first-line ophthalmological
443 treatments were assessed.

444 The study strenght could be the ophthalmological follow-up that allowed assessing the long-
445 term results of the therapeutic options.

446
447 **In summary**, local corticosteriod injections for uveitis seem to be associated with favorable
448 visual outcomes while continuing CIT. They could be suggested as a first-line therapy for the
449 management of CIT-associated uveitis.

450 Ophthalmologists should explain the often favorable visual outcome of CIT-associated uveitis
451 when treated early with local corticosteroids, reassure patients and the care team, explain the
452 expected rapid visual improvement and the possible occurrence of AEs, including cataract and
453 glaucoma, and regularly check corticosteroid efficacy and AEs. In case of failure, they should
454 early adapt treatment after collegial discussion on a case-by-case basis.

455 456 **Conclusion**

457 The long-term ophthalmological and systemic assesements of patients with CIT-associated
458 uveitis described in this series together with literature data suggest to use local corticosteroid
459 injections as a first line while CIT is continued. The ophthalmological interventions should be
460 given early not to alter patients' quality of life. Indeed, preserving the quality of life could be
461 a new important challenge for the numerous patients treated with CIT, and represent a huge
462 progress in terms of survival outcomes. Uveitis treatment could maintain the quality of life
463 while not impairing the expected outcome of CIT on tumor mass increase. An adapted uveitis
464 management could improve the visual prognosis, without impairing the vital prognosis.

465
466
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656

657 **Figure captions**

658 Figure 1: Patient 1. 81-year old woman treated with rituximab for 4 months for chronic
659 lymphoid leucemia and referred for visual loss of her only functional eye (RE) due to macular
660 edema complicating intermediate uveitis. The left eye showed former corneal scars. 1A
661 OCT of the RE: cysts mainly located in the inner nuclear layer. 1B OCT of the RE: 1 month
662 after sub-Tenon's triamcinolone injection, the macular edema disappeared, the visual acuity
663 improved from 0.2 to 0 LogMAR.

664

665 Figure 2: Patient 2. An 88-year old man previously treated for Waldstrom disease,
666 experienced 3 years later a metastatic dermic-hypodermic sarcoma treated with ibrutinib and

667 cyclophosphamide. Eighteen months later, a bilateral visual loss was reported due to
668 panuveitis associated with bilateral macular edema and multifocal peripheral nodular
669 choroidal lesions. Both eyes showed similar lesions. RE : 2A wide field retinography showing
670 peripheral nodular lesions 2B FA 10 min after dye injection, showed a leakage in the central
671 macular area and papillitis 2C: ICGA 4 min after dye injection, showed numerous
672 hypofluorescent nodular lesions 2D they disappeared at 30 min, suggesting an inflammatory
673 activity although an effect of masking by the normal staining of the retinal pigmentary
674 epithelium at 10 minutes may interfere. 2E OCT showing macular cysts mainly located in the
675 inner nuclear layer. 2F the macular edema resolved after treatment with systemic
676 corticosteroids for 6 months in both eyes.

677
678

679 Figure 3: Patient 3. 61-year old man treated with nivolumab, dabrafenib, and trametinib for a
680 BRAF V600E mutation-positive melanoma. Intermediate uveitis complicated by macular
681 edema occurred 18 months after treatment discontinuation due to cryoglobulinemia and
682 pneumopathy. The peripheral isopters of the visual field remained normal and the etiological
683 work-up was negative. In particular, the aqueous humor testing showed a cytokine profile
684 consistent with an inflammatory or infectious process (IL-10 at 3 pg/mL and IL-6 at 105
685 pg/mL). The Herpes virus PCR was negative. Diagnostic vitrectomy showed the presence of
686 pigmented histiocytes, a few lymphocytes and the absence of malignant cells. The anti-
687 recoverin antibody assay was negative. Both eyes showed similar lesions. RE : 3A: wide-field
688 retinography. 3B: autofluorescence showing a shadowing of the inflammatory vitreous. 3C:
689 OCT showed macular edema cysts located mainly in the inner nuclear layer. 3D: A sub-
690 Tenon's triamcinolone injection was effective, the macular cysts disappeared and the visual
691 acuity improved from 0.2 to 0.1 LogMAR.

692

693 Figure 4: Patient 4. A 63-year old woman with KRAS-mutant bronchial adenocarcinoma (T3,
694 N3, M1b) was treated with nivolumab and bevacizumab for more than one year. She
695 experienced a bilateral visual loss due to bilateral panuveitis associated with macular edema
696 and focal choroidal nodular lesions. Both eyes showed similar lesions. RE 4A retinography
697 showing papillitis and peripheral nodular lesions. 4B: OCT horizontal scan showing cysts in
698 the inner nuclear layer. 4C: autofluorescence showing nodular hyperautofluorescent
699 lesions. 4D: FA showing a papillary and macular leakage and cyst filling. 4E: ICGA showing
700 numerous focal hypofluorescent nodular lesions, well visible at 10 minutes. 4F: they
701 disappeared during the late phase (30 min).

702

703 Figure 5: Patient 5. A 75-year old woman was treated with nivolumab for metastatic pleural
704 mesothelioma for 4 months when a bilateral visual loss occurred, due to acute anterior uveitis
705 with hypopyon, successfully treated with dexamethasone subconjunctival injections. In the
706 RE, hypopyon complicating acute anterior uveitis.

707

Figure 1

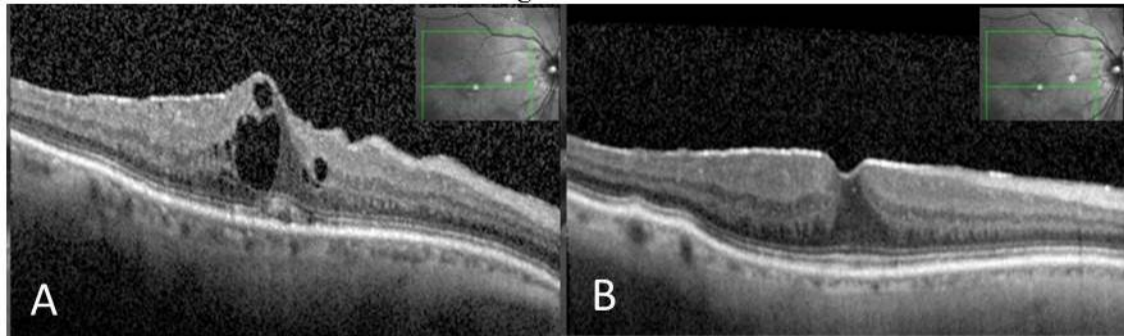
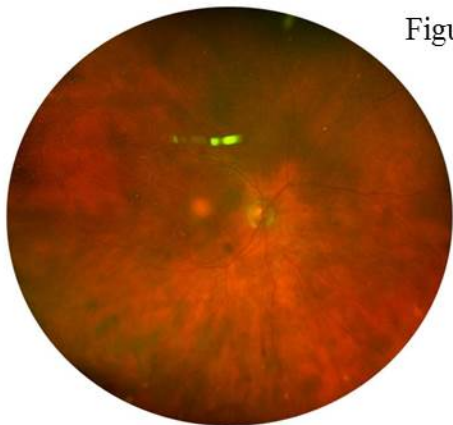
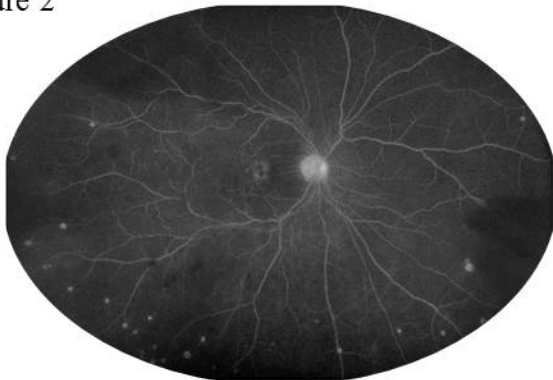


Figure 2

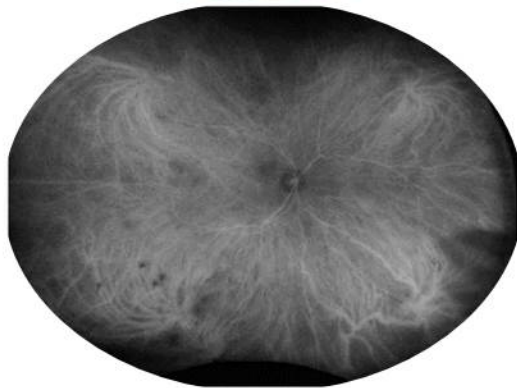
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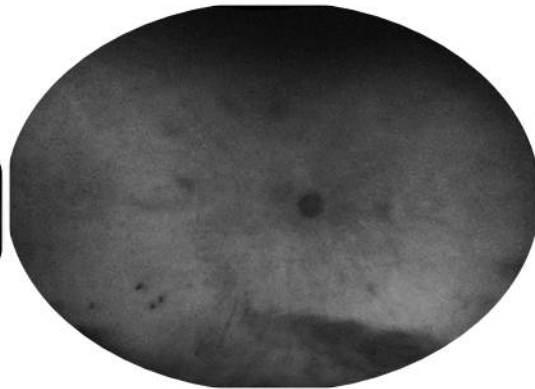
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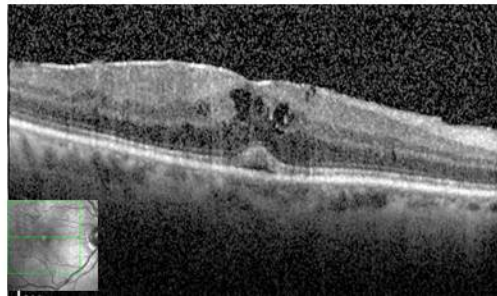
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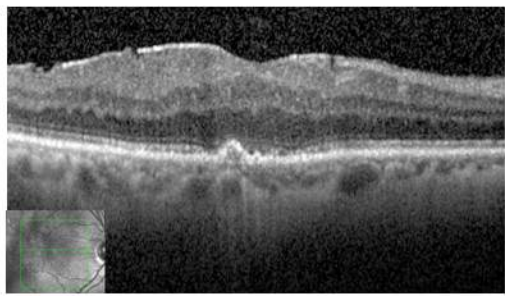
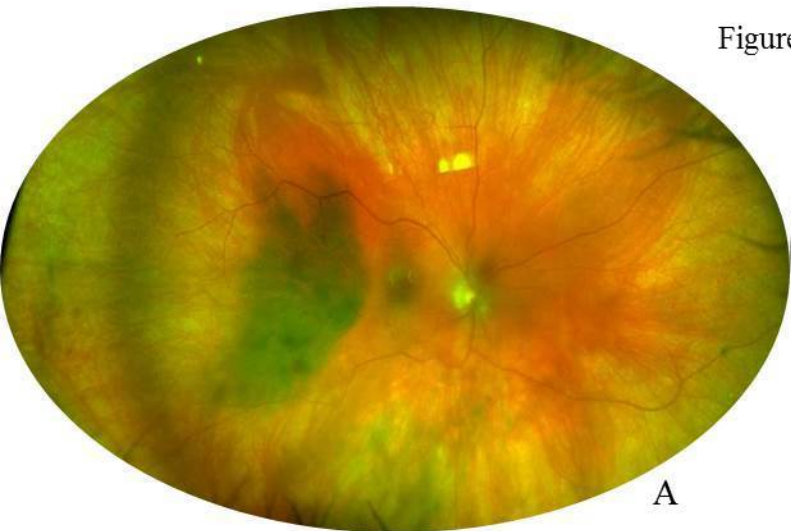
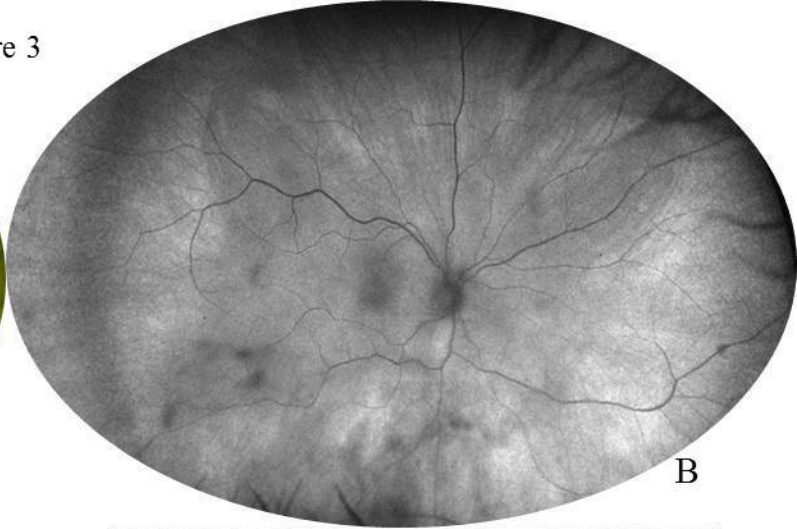


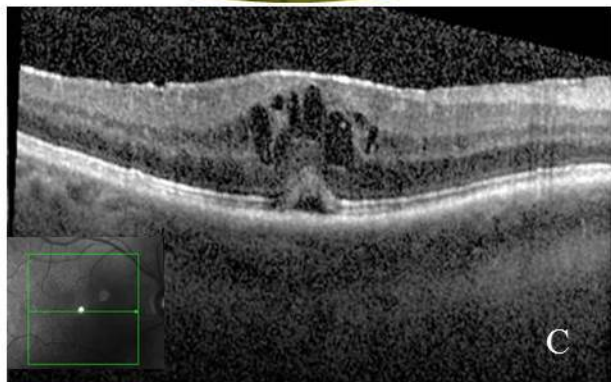
Figure 3



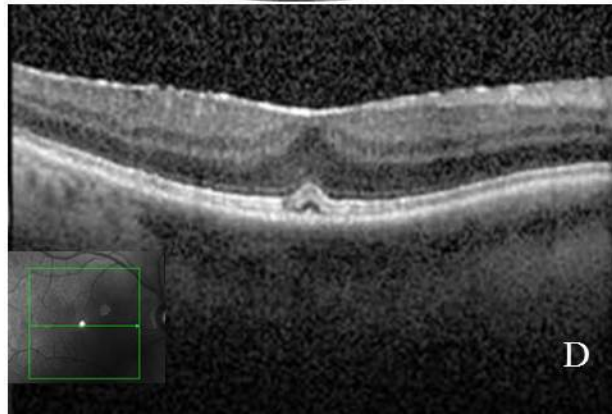
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Figure 4

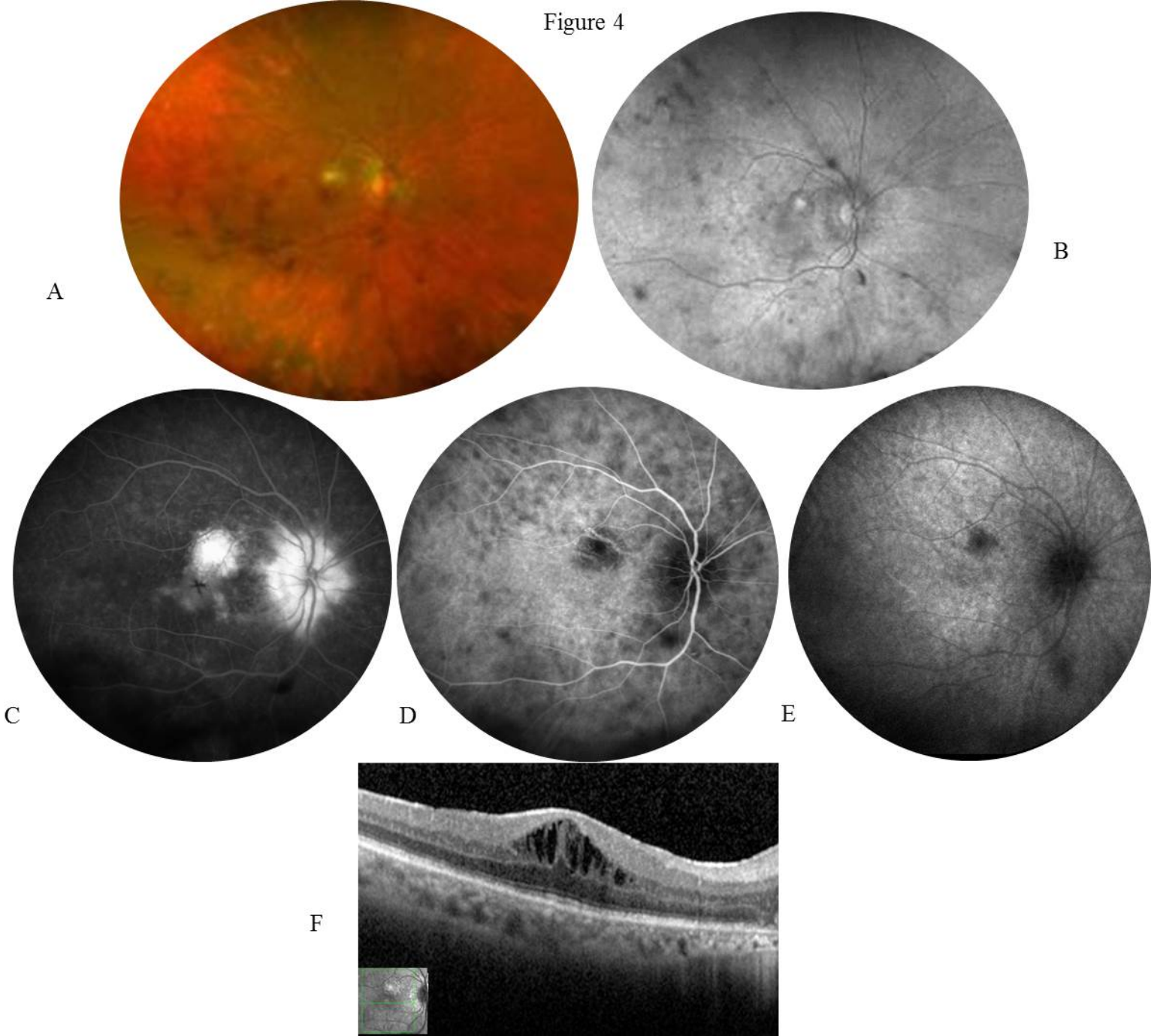
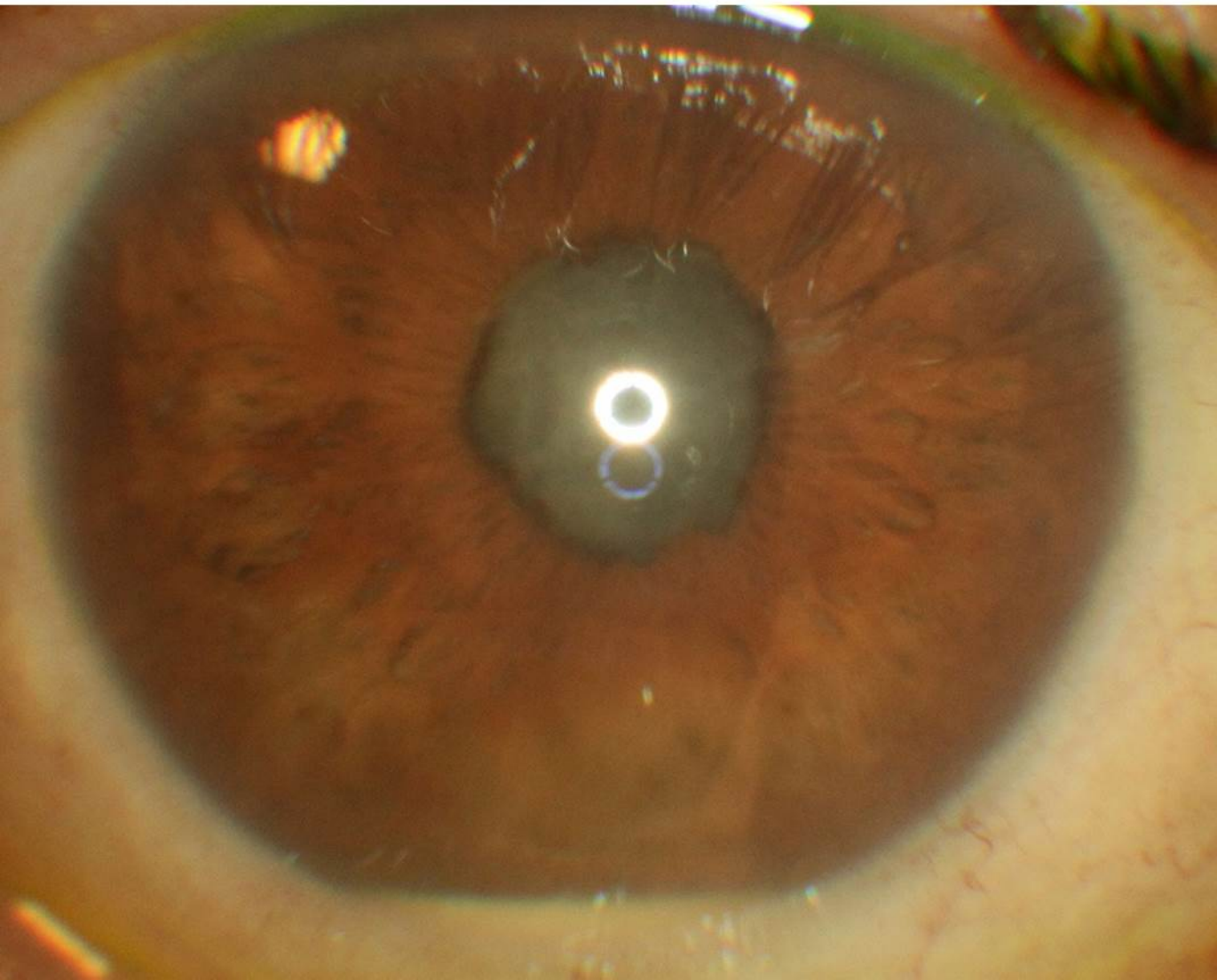


Figure 5



1st therapeutic intervention2nd intervention

| Patient number, gender and age at uveitis onset | Neoplasia grading | CIT type | Time between ICI initiation and uveitis onset (months) | Oncological response | Baseline visual acuity in the RE/LE in decimals and LogMAR | Active uveitis features | CIT discontinuation | Ophthalmological treatments | Visual acuity at 3 months RE/LE LogMAR | Favorable ophthalmological outcome at 3 months | CIT resumption | Uveitis activity at 12 months | Final outcome at 12 months |
|---|---|--|--|----------------------|--|---|-----------------------------------|---|--|--|---|--|----------------------------|
| 1 F. 81 | Chronic lymphoid leukemia | Rituximab (Anti-CD20) | 4 | CR | 0.6/0.01 0.2/2 | Bilateral intermediate Uveitis and ME | yes | Local corticosteroids Sub-Tenon's triamcinolone injection | 0/2 | Yes | Resumption after 3 years for leukemia recurrence | No | Alive CR |
| 2 M. 72 | Less differentiated sarcoma in Waldenström disease | Ibrutinib (Bruton tyrosine Kinase inhibitor) | 18 | PR | 0.5/0.5 0.3/0.3 | Bilateral panuveitis choroiditis and ME | no | Systemic corticosteroids | 0.2/0.1 | Yes | ongoing | No | Alive PR |
| 3 M. 61 | Stage 4 BRAF V600E mutation-positive melanoma | Nivolumab (Anti-PD-1) + Dabrafenib (Anti-BRAF) + Trametinib (Anti-MEK) | 24 | PR | 0.8/0.8 0.1/0.1 | Bilateral intermediate uveitis and ME | no | Sub-Tenon's triamcinolone injection | 0.2/0.2 | yes | ongoing | Yes Good VA with triamcinolone injections | Alive CR |
| 4 F. 65 | T3 lung adenocarcinoma | Nivolumab (Anti-PD-1) | 13 | PR | 0.5/0.7 0.3/0.2 | Bilateral panuveitis choroiditis and ME | no | Dexamethasone subconjunctival injections | 0.1/0.1 | yes | ongoing | Yes Bilateral ME | Death |
| 5 F. 74 | Pleural mesothelioma | Nivolumab (Anti-PD-1) | 4 | CR | 0.01/0.01 2/2 | Bilateral anterior uveitis Bilateral hypopion | yes | Local antibiotics and dexamethasone drops Dexamethasone subconjunctival injections | 0/0 | Yes | Resumption after 6 months for tumor mass increase | No | Death |
| 6 F. 83 | Melanoma | Nivolumab (Anti-PD-1) | 5 | CR | 0.8/0.1 0.1/1 | Bilateral posterior uveitis Papillary edema Contiguous ME | Yes for interstitial pneumonitis | Systemic corticosteroids | 0/0.3 | no | no | no | Alive PR |
| 7 M. 58 | BRAF V600E mutation-positive superficial spreading melanoma | Vemurafenib (Anti-BRAF) | 5 | CR | 0.6/0.8 0.2/0.1 | Bilateral anterior uveitis | Yes for peripheral neuropathy | Local corticosteroids Dexamethasone drops | 0/0 | yes | Yes with nivolumab | no | Alive CR |
| 8 M. 59 | Stage 4 BRAF V600E mutation-positive melanoma | Nivolumab + Ipilimumab (Anti-CTLA-4) | 1 | PR | 1.0/1.0 0/0 | Bilateral anterior uveitis | Yes ipilimumab discontinuation | Local corticosteroids Dexamethasone drops | 0/0 | yes | Yes with nivolumab | No at 3 months | Alive PR at 3 months |

CIT: Cancer ImmunoTherapy; PR: Partial response; CR: complete response; ME: macular edema; OPH:

| Patient | Baseline uveitis features | Corneal precipitates | Post synechiae | Hypopyon | IOP >21 mmHg | Vitreous cells grading RE/LE | Flare Photon/ms RE/LE | Macular edema | Central foveal thickness Microns RE/LE | FA and ICGA findings | Uveitis grading CTCAE |
|---------|--------------------------------|----------------------|----------------|----------|--------------|------------------------------|-----------------------|---------------|--|---|-----------------------|
| 1 | Bilateral intermediate uveitis | fine | NO | NO | NO | ++/+ | 8.4/ND | YES | 462/ND | Retinal peripheral venous leakage Papillitis | 3 |
| 2 | Bilateral panuveitis | Small granulomatous | NO | NO | NO | +/+ | 26.2/16.6 | YES | 441/483 | Retinal edematous capillaritis Choroidal nodular lesions | 3 |
| 3 | Bilateral intermediate uveitis | fine | YES | NO | NO | ++/+++ | 108.1/315.3 | YES | 500/399 | Macular leakage | 3 |
| 4 | Bilateral panuveitis | Small granulomatous | YES | NO | NO | ++/+++ | 44.9/50.4 | YES | 455/410 | posterior pole leakage Choroidal nodular lesions | 3 |
| 5 | Bilateral anterior uveitis | fine | YES | YES | NO | +/+ | 152.3/64.7 | NO | 282/259 | ND | 4 |
| 6 | Bilateral posterior uveitis | fine | NO | NO | NO | +/+ | 3.1/3.9 | YES | 295/360 | Papillitis | 4 |
| 7 | Bilateral anterior uveitis | fine | YES | NO | NO | ½+/½+ | 23.5/25.4 | NO | 275/269 | ND | 2 |
| 8 | Bilateral anterior uveitis | fine | NO | NO | NO | ½+/½+ | nd | NO | 248/250 | Papillary edema | 1 |

CTCAE: Common terminology criteria for adverse events; ND: not determined; IOP: intraocular pressure

| Posterior segment involvement | Posterior segment involvement features | CIT drug(s) | Number of cases | Corticosteroid type (local/systemic/topical) (local=IVT , subTenonien injections) | CIT drug stop | Uveitis resolution after therapeutic intervention |
|-------------------------------|--|--------------------------------------|-----------------|---|--------------------------------|---|
| Wong et al. 2012 | VKH-like | ipilimumab | 1 | Systemic | Yes | Yes |
| Crosson et al. 2015 | VKH-like | ipilimumab | 1 | None | No | ND |
| Fierz et al. 2016 | Papillary edema Choroidal nodular lesions | ipilimumab | 1 | Systemic | Yes | No |
| Robinson et al. 2004 | ME and papillitis | ipilimumab | 1 | Local | Yes | Yes |
| Tsui et al. 2019 | ME and retinal vasculitis | ipilimumab | 1 | Local and systemic | Yes | Yes |
| Sun et al. 2019 | CME Panuveitis | ipilimumab ipilimumab + nivolumab | 2 2 | Periocular triam/topical Local | ND ND | Yes / no Yes / no |
| Conrady et al. 2018 | Subretinal fluid Multifocal choroiditis | ipilimumab + nivolumab | 2 | Systemic/local | Yes | Yes |
| Conrady et al. 2018 | Central retinal artery occlusion Multifocal choroiditis | ipilimumab + nivolumab | 1 | Systemic | ND | No |
| Venkat et al. 2019 | Papillitis and peripheral leakage on FA | ipilimumab + nivolumab | 1 | Local | Yes Ipilimumab discontinued | Yes |
| Obata et al. 2019 | VKH-like Granulomatous corneal precipitates Choroidal granulomas | nivolumab | 1 | Local IVT | Yes | Yes |
| Arai et al. 2017 | VKH-like | nivolumab | 1 | Local | Yes | |
| Theillac et al. 2017 | ME, papillary edema Granulomatous corneal precipitates | nivolumab | 1 | Systemic | Yes | Yes |
| Wei et al. 2019 | Serous retinal detachment | nivolumab | 1 | Local and systemic IVT DXM implant | Yes | Yes |
| De Velasco et al. 2016 | CME | nivolumab | 1 | Intraocular steroids | No | Yes |
| Richardson et al. 2017 | ME and papillitis | nivolumab | 1 | Local IVT | Yes | Yes |
| Conrady et al. 2018 | Subretinal fluid Multifocal choroiditis | nivolumab | 1 | Local | ND | Yes |
| Sun et al. 2019 | Panuveitis | nivolumab | 1 | Local | ND | Yes |
| Fujimura et al. 2018 | VKH-like | Nivolumab + dabrafenib/trametinib | 2 | Systemic | Yes | Yes |
| Matsuo et al. 2017 | VKH-like | Nivolumab + vemurafenib | 1 | Systemic | Yes | Yes |
| Bitton et al. 2019 | Subretinal fluid | pembrolizumab | 1 | Systemic | Yes | Initial improvement and then relapse |
| Sun et al. 2019 | Panuveitis | pembrolizumab | 2 | Local | ND | Yes / no |
| Conrady et al. 2018 | ME | pembrolizumab | 1 | Local IVT | ND | Yes |
| Aaberg et al. 2017 | Posterior uveitis, retinal vasculitis | pembrolizumab | 1 | Local IVT | No | Yes |
| Hanna et al. 2016 | Panuveitis Multifocal choroiditis | pembrolizumab | 1 | Local and systemic | Yes | Yes |
| Diem et al. 2016 | panuveitis | pembrolizumab | 1 | Systemic | Yes | Yes |
| Manusow et al. 2014 | Retinal vasculitis | pembrolizumab | 1 | Local and systemic | No | Yes |
| Abu et al. 2016 | Papillitis | pembrolizumab | 1 | Local | ND | Yes |
| Bricout et al. 2017 | VKH-like | pembrolizumab | 1 | Systemic | ND | Yes |
| Reid et al. 2019 | Optic disc edema hypotony | pembrolizumab | 1 | Systemic | Yes | No |
| Whist et al. 2019 | hypotony | pembrolizumab | 1 | Systemic | Yes | No |
| Venkat et al. 2019 | ME and peripheral leakage on FA | atezolizumab | 1 | Local IVT | Yes | Yes |
| Conrady et al. 2018 | Retinal vasculitis | atezolizumab | | Systemic | | Yes |
| Guedj et al. 2014 | ME | vemurafenib | 1 | Systemic | Yes | No |
| Fierz et al. 2016 | Retinal vasculitis | vemurafenib | 1 | Local | Yes | Yes |
| Whist et al. 2019 | ME | vemurafenib | 1 | Local | No | Yes |
| Fonollosa et al. 2015 | ME | vemurafenib | 1 | ND | ND | Yes |
| Gavric et al. 2018 | ME Subretinal fluid | Vemurafenib + cobimetinib | 1 5 | Topical | ND | ND |
| Whist et al. 2019 | ME | Dabrafenib + trametinib | 4 | Systemic | ND | Yes |
| Draganova et al. 2015 | Multiple subretinal detachment | Dabrafenib + trametinib | 1 | | Yes | Yes |
| Sarny et al. 2017 | ME and focal lesions | Dabrafenib + trametinib | 1 | ND | Yes | Yes |
| Joshi et al. 2013 | Panuveitis | Dabrafenib + trametinib | 1 | ND | Yes | Yes |
| Flaherty et al. 2012 | RPE detachment | trametinib | 1 | | Yes | Yes |
| Mirgh et al. 2020 | ME | ibrutinib | 1 | Local | ND | Yes |
| Bussone et al. 2010 | ME | rituximab | 2 | Systemic | ND | ND |
| Gilca et al. 2019 | ME | rituximab | 1 | Systemic followed by local | Yes | Yes |
| Juric et al. 2021 | ME | Rituximab | 1 | Local | ND | yes |

IVT: intravitreal therapy; Triam: triamcinolone; CME: cystoid macular edema; ME: macular edema; ND: not determined; RPE: retinal pigmentary epithelium; FA: fluorescein angiography; VKH: Vogt-Koyanagi-Harada disease; DXM dexamethasone