Supplemental Information: Protocol for systematic review

**Title:** Autoimmune retinopathy with associated anti-retinal antibodies as a potential immune-related adverse event associated with immunotherapy in patients with advanced cutaneous melanoma: case series and systematic review

**Registration:** None

**Amendments:** None

**Introduction**

**Rationale:** Immune-related adverse events (irAEs) are common after the initiation of immunotherapy for advanced cutaneous melanoma. Autoimmune retinopathy (AIR) is an underappreciated irAE in this context.

**Objective:** To demonstrate the spectrum of autoimmune retinopathy (AIR) following immunotherapy for advanced cutaneous melanoma

**Methods**

**Inclusion criteria**
- PubMed indexed
- Written in English
- Visual symptoms began after the initiation of immunotherapy for cutaneous or non-ocular mucosal melanoma
- Clinical evidence of autoimmune retinopathy

**Exclusion criteria**
- Immunotherapy for malignancies other than cutaneous or non-ocular mucosal melanoma
- Onset of visual symptoms or ocular findings prior to initiation of immunotherapy

**Information source(s):** PubMed

**Search strategy:** Searches were carried out with the following search terms: “melanoma” AND (“retinopathy” OR “maculopathy”) AND (“immunotherapy” OR “checkpoint inhibitor” OR “pembrolizumab” OR “nivolumab” OR “ipilimumab”)

**Data management:** Records will be stored in an Excel spreadsheet

**Selection process:** Studies will be screened and assessed for eligibility by a single reviewer. Studies selected for inclusion are then reviewed by two independent reviewers.
**Data collection process:** Data will be collected in a spreadsheet

**Variables sought:**
- Patient’s sex
- Patient’s age
- Immunotherapy at the onset of visual symptoms
- Visual symptoms
- Onset of visual symptoms after initiation of immunotherapy
- BCVA at presentation
- Ocular finding(s)
- Anti-retinal antibodies detected
- Concurrent systemic irAE
- Treatment for AIR
- Cessation of immunotherapy
- Duration of follow-up

**Outcome measures:**
- Ocular outcome
- Systemic outcome if reported

**Risk of bias in individual studies:**
Bias in individual studies can be presumed from omission of ocular outcomes. Studies with unexplained omission of ocular outcomes will be excluded from the final data synthesis.

**Data synthesis:**
Simple percentages of outcome measures will be reported. For measures involving time, median and interquartile range will be reported. Missing data will be reported as “not reported”. The synthesized data will be presented in a table.
Supplemental Figure 1. Systematic review flow diagram

Identification of new studies via databases and registers

- Records identified from:
  - Databases (n = 1)
  - Registers (n = 0)

- Records removed before screening:
  - Duplicate records (n = 0)
  - Records marked as ineligible by automation tools (n = 0)
  - Records removed for other reasons (n = 0)

- Records screened (n = 53)
- Records excluded (n = 33)

- Reports sought for retrieval (n = 20)
- Reports not retrieved (n = 0)

- Reports assessed for eligibility (n = 20)
  - Reports excluded:
    - Immunotherapy for malignancies other than cutaneous or non-ocular mucosal melanoma (n = 1)
    - Onset of visual symptoms or ocular findings prior to immunotherapy initiation (n = 5)

- New studies included in review (n = 13)
- Reports of new included studies (n = 0)

Identification of new studies via other methods

- Records identified from:
  - Websites (n = 0)
  - Organisations (n = 0)
  - Citation searching (n = 0)

- Reports sought for retrieval (n = 0)
- Reports not retrieved (n = 0)

- Reports assessed for eligibility (n = 0)
  - Reports excluded: 0 (n = 0)
### Supplemental Table 1. Summary of published cases in systematic review

<table>
<thead>
<tr>
<th>Publication</th>
<th>Sex</th>
<th>Age</th>
<th>Immuno-therapy</th>
<th>Visual symptom(s)</th>
<th>Symptom onset after starting immuno-therapy</th>
<th>BCVA at presentation</th>
<th>Ocular finding(s)</th>
<th>Anti-retinal antibodies detected</th>
<th>Concurrent systemic irAE</th>
<th>Treatment</th>
<th>Immuno-therapy stopped</th>
<th>Ocular outcome</th>
<th>Systemic outcome</th>
<th>Duration of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mantopoulos et al. 2015 [22]</td>
<td>F</td>
<td>Early 70s</td>
<td>Ipilimumab for CM</td>
<td>Unspecified vision loss, photophobia</td>
<td>12 weeks</td>
<td>6/12 OD, 6/12 OS</td>
<td>Acute exudative polymorphous vitelliform maculopathy OU</td>
<td>Not tested</td>
<td>Pruritis</td>
<td>Topical corticosteroids, oral corticosteroids</td>
<td>Yes</td>
<td>Complete resolution; 6/7.5 OD, 6/7.5 OS</td>
<td>Not reported</td>
<td>6 months</td>
</tr>
<tr>
<td>Crews et al. 2015 [23]</td>
<td>M</td>
<td>46</td>
<td>Ipilimumab for CM</td>
<td>Unspecified vision loss, photophobia</td>
<td>6 weeks</td>
<td>6/30 OD, 6/30 OS</td>
<td>Serous retinal detachments OU</td>
<td>Not tested</td>
<td>Transaminitis</td>
<td>IV corticosteroids</td>
<td>Yes</td>
<td>Partial resolution; 6/18 OD, 6/12 OS</td>
<td>Not reported</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Theillac et al. 2017 [24]</td>
<td>M</td>
<td>55</td>
<td>Nivolumab for CM</td>
<td>Blurred vision</td>
<td>6 weeks</td>
<td>6/6 OD, 6/12 OS</td>
<td>Bilateral granulomatous anterior uveitis, bilateral papillitis, serous retinal detachment OS</td>
<td>Not tested</td>
<td>No reported</td>
<td>Oral corticosteroids, topical corticosteroids</td>
<td>Yes</td>
<td>Complete resolution; BCVA 6/6 OU</td>
<td>Not reported</td>
<td>1 month</td>
</tr>
<tr>
<td>Tsui et al. 2017 [25]</td>
<td>M</td>
<td>Late 60s</td>
<td>Ipilimumab, Nivolumab for CM</td>
<td>Unspecified vision loss, photopia</td>
<td>5 weeks</td>
<td>6/45 OD, 6/45 OS</td>
<td>Serous retinal detachments and choroidal detachments OU</td>
<td>Not tested</td>
<td>No reported</td>
<td>Oral corticosteroids</td>
<td>Yes</td>
<td>Partial resolution of serous RDs and choroidal effusion; 6/15 OD, 6/12 OS</td>
<td>Not reported</td>
<td>7 weeks</td>
</tr>
<tr>
<td>Acaba-Berrocal et al. 2018 [26]</td>
<td>F</td>
<td>65</td>
<td>Pembrolizumab for CM</td>
<td>Blurred vision</td>
<td>2 years</td>
<td>6/12 OD, 6/30 OS</td>
<td>Birdshot-like choriotrephopathy OU</td>
<td>Not tested</td>
<td>No reported</td>
<td>subTenon’s triamcinolone injection OU</td>
<td>Not reported</td>
<td>Partial resolution; BCVA 6/12 OD, 6/18 OS</td>
<td>Not reported</td>
<td>6 months</td>
</tr>
<tr>
<td>Sandhu et al. 2019 [27]</td>
<td>F</td>
<td>55</td>
<td>Ipilimumab, pembrolizumab (+ trametinib + vemurafenib) for CM</td>
<td>Blurring of central vision</td>
<td>7 months</td>
<td>6/12 OD, 6/12 OS</td>
<td>Acute exudative polymorphous vitelliform maculopathy OU</td>
<td>Not tested</td>
<td>No reported</td>
<td>Topical corticosteroids, dorzolamide</td>
<td>Yes</td>
<td>Complete resolution; BCVA 6/6 OD, 6/7.5 OS</td>
<td>POD</td>
<td>4 months</td>
</tr>
<tr>
<td>Golash et al. 2020 [28]</td>
<td>F</td>
<td>82</td>
<td>Pembrolizumab for CM</td>
<td>Blurred vision</td>
<td>3 days</td>
<td>6/12 OD, 6/18 OS</td>
<td>Serous retinal detachments and choroidal detachments OU, panuveitis OU, hypopyon OU</td>
<td>Not tested</td>
<td>None</td>
<td>Topical corticosteroids, oral steroids, cataract surgery with intravitreal dexamethasone implant OU</td>
<td>Not reported</td>
<td>Initial decline to CF OD, 2/36 OS; Partial resolution. 6/24 OD, 6/24 OS</td>
<td>Not reported</td>
<td>6 months</td>
</tr>
<tr>
<td>Kemels et al. 2020 [29]</td>
<td>M</td>
<td>74</td>
<td>Nivolumab for NOMM</td>
<td>Unspecified vision loss</td>
<td>3 weeks</td>
<td>6/7.5 OD, 6/9.5 OS</td>
<td>Acute exudative polymorphous vitelliform maculopathy OU</td>
<td>Not tested</td>
<td>No reported</td>
<td>Oral corticosteroids</td>
<td>Yes</td>
<td>No reported change in vision</td>
<td>POD</td>
<td>1 month</td>
</tr>
<tr>
<td>Kemels et al. 2020 [29]</td>
<td>F</td>
<td>51</td>
<td>Nivolumab for NOMM</td>
<td>Unspecified visual loss, photopia</td>
<td>1 month</td>
<td>6/9.5 OD, 6/6 OS</td>
<td>Acute exudative polymorphous vitelliform maculopathy OU</td>
<td>Not tested</td>
<td>No reported</td>
<td>Sarcoid-like granulomatous reaction</td>
<td>Periocular corticosteroids OU, intravitreal corticosteroid implants OU, resection of primary tumor</td>
<td>Yes</td>
<td>Partial resolution, 6/7.5 OD, 6/7.5 OS</td>
<td>PR</td>
</tr>
<tr>
<td>Publication</td>
<td>Sex</td>
<td>Age</td>
<td>Immuno-therapy</td>
<td>Visual symptom(s)</td>
<td>Symptom onset after starting immuno-therapy</td>
<td>BCVA at presentation</td>
<td>Ocular finding(s)</td>
<td>Anti-retinal antibodies detected</td>
<td>Concurrent systemic irAE</td>
<td>Treatment</td>
<td>Immuno-therapy stopped</td>
<td>Ocular outcome</td>
<td>Systemic outcome</td>
<td>Duration of follow-up</td>
</tr>
<tr>
<td>------------</td>
<td>-----</td>
<td>-----</td>
<td>----------------</td>
<td>------------------</td>
<td>--------------------------------------------</td>
<td>---------------------</td>
<td>------------------</td>
<td>-------------------</td>
<td>-------------------</td>
<td>-----------</td>
<td>-------------------</td>
<td>---------------</td>
<td>-------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Miyamoto et al. 2020 [30]</td>
<td>M</td>
<td>73</td>
<td>Nivolumab for NOMM</td>
<td>Metamorphopsia OU</td>
<td>2 months</td>
<td>6/6</td>
<td>6/4.8</td>
<td>Acute exudative polymorphous vitelliform maculopathy OU</td>
<td>Not tested</td>
<td>Not reported</td>
<td>None</td>
<td>No</td>
<td>No follow up</td>
<td>POD</td>
</tr>
<tr>
<td>Elwood et al. 2021 [31]</td>
<td>F</td>
<td>65</td>
<td>Ipilimumab, Nivolumab for CM</td>
<td>Photopsia, visual field loss</td>
<td>18 months</td>
<td>6/12</td>
<td>6/15</td>
<td>MAR OU, chorooretinal leakage OU, venous leakage on FA OU, occult CNV OD</td>
<td>Anti-60 kDa retinal protein</td>
<td>Adrenal insufficiency</td>
<td>Intravitreal bevacizumab OD, subTenon’s triamcinolone injection OS</td>
<td>Yes</td>
<td>Complete resolution of subretinal fluid OD, initial decline in BCVA OS to CF, partial resolution after subTenon’s triamcinolone OS; improvement of visual field defects; BCVA 6/7.5 OD, 6/30 OS</td>
<td>Not reported</td>
</tr>
<tr>
<td>Whist et al. 2021 [32]</td>
<td>M</td>
<td>30</td>
<td>Ipilimumab + nivolumab for CM</td>
<td>Photopsia, floaters, nyctalopia</td>
<td>5 months</td>
<td>6/6</td>
<td>6/6</td>
<td>MAR OU; anterior &amp; intermediate uveitis, CME, retinal periphlebitis OU</td>
<td>Not tested</td>
<td>Autoimmune hepatitis</td>
<td>IV and oral corticosteroids, mycophenolate, infliximab</td>
<td>Yes</td>
<td>No change in ERG deficits; BCVA 6/6 OD</td>
<td>Not reported</td>
</tr>
<tr>
<td>Lambert et al. 2021 [33]</td>
<td>F</td>
<td>54</td>
<td>Pembrolizumab for NOMM</td>
<td>Blurred vision, photopsia</td>
<td>3 months</td>
<td>6/6</td>
<td>6/6</td>
<td>Acute exudative polymorphous vitelliform maculopathy OU</td>
<td>Not tested</td>
<td>Autoimmune thyroiditis, Sarcoid-like granulomatous reaction</td>
<td>None</td>
<td>Yes</td>
<td>Complete resolution of subretinal fluid</td>
<td>PR</td>
</tr>
<tr>
<td>Yilmaz Tugan et al. 2021 [34]</td>
<td>M</td>
<td>60</td>
<td>Nivolumab for CM</td>
<td>Blurred vision</td>
<td>7 weeks</td>
<td>CF</td>
<td>CF</td>
<td>Serous retinal detachment OU, anterior uveitis OU</td>
<td>Not tested</td>
<td>Not reported</td>
<td>Oral corticosteroids, topical corticosteroids</td>
<td>No</td>
<td>Complete resolution, BCVA 6/6, 6/9.5</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

CM = cutaneous melanoma; NOMM = non-ocular mucosal melanoma; MAR = melanoma-associated retinopathy; PR = partial response CR = complete response; POD = progression of disease