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Severe Ocular Adverse Reaction Following Single Pembrolizumab Infusion: A Case Report

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1. Abstract

1.1. Purpose: To report a case of severe sight loss following single infusion of pembrolzumab

1.2. Methods: Retrospective case report

1.3. Results: Ocular adverse events associated with immune checkpoint inhibitors, due to their rarity, remain poorly characterised. Pembrolizumab targets the programmed cell death (PD-1) protein on T cells, circumventing the mechanisms by which cancer cells evade the body's adaptive immune response. To date, reports of ocular surface disease, neuro-ophthalmic complications, orbitopathy, retinal dysfunction and uveitis have been reported following pembrolizumab infusion. We report the first case of severe panuveitis resulting in loss of vision, following a single initial infusion of pembrolizumab.

1.4. Conclusion: The case serves as a heartening reminder of the need for prompt reporting of visual symptoms, recognition of ocular immune-related adverse events and a multi-disciplinary approach between oncology and ophthalmology in patients receiving immunotherapy for cancer treatment.

2. Background

Pembrolizumab was approved as a first-line therapeutic agent for unresectable or metastatic squamous cell carcinoma of the head and neck by NICE in 2020 [1]. Since then, it has been a central treatment option for a cohort of patients who were previously limited to a small selection of chemotherapy agents. An IgG4 monoclonal antibody targeting the programmed cell death (PD-1) protein on T cells, pembrolizumab acts to circumvent the mechanisms by which cancer cells evade the body's adaptive immune response. Though reportedly better tolerated than pre-existing chemotherapy drugs [2], much remains unknown about immune-related adverse events that it may precipitate. To date, pneumonitis, hepatitis, colitis, hypothyroidism, and cutaneous adverse events have all been widely reported following pembrolizumab treatment [3]. Ocular adverse events, though reported less frequently, must also be considered, as our case demonstrates.

3. Case Report

A 78 year-old male was diagnosed with a locally advanced squamous cell carcinoma of the oral cavity in 2020. He had a large primary arising from the right tongue with associated bilateral lymphadenopathy. Radical surgery and reconstruction would have been extensive, and he was not fit enough for this. He underwent a short course of palliative radiotherapy to the macroscopic disease with a margin only, and a complete clinical response was achieved. The radiotherapy field did not approach the eyes (Figure 1). In 2023, he reported worsening symptoms, including dysphagia and right-sided facial swelling. Serial imaging confirmed radiological progression and he was commenced on first-line palliative immunotherapy with pembrolizumab. His past medical history was otherwise unremarkable, and his past ocular history included previous left eye cataract surgery only. On the evening following his first pembrolizumab infusion, he developed a severe headache, followed by left eye redness, periocular swelling and blurring of vision, progressing to complete loss of vision in the left eye two

days later. He presented to the Emergency Department three days after the infusion, at which time he had severe left eye pain and loss of vision. On examination, he was afebrile and systemically well. His Snellen visual acuity was 6/9 in the right eye, and no perception of light in the left eye. He had no proptosis and intraocular pressures were normal. There was marked left eyelid swelling, conjunctival chemosis, redness (Figure 2), and an intense fibrinous and haemorrhagic inflammatory reaction in the anterior chamber with small hypopyon. A haemorrhagic vitreous opacity obscured the view of the retina. The right eye exam was unremarkable, with healthy retina and optic nerve. Ultrasound B scan of the left eye was suggestive of haemorrhagic choroidal effusions and scleritis. Blood tests revealed a white cell count 8.4 $x10^9$/L, platelets 475 $x10^9$/L, CRP 34mg/L and albumin of 30g/L. MRI imaging indicated inflammatory change throughout the left orbit associated with a haemorrhagic choroidal effusion. On admission, intravenous antibiotics (metronidazole and ceftriaxone) were commenced, with an initial working diagnosis of orbital cellulitis with possible intraocular infection. Intravitreal injection of vancomycin and ceftazidime was administered and a sample of vitreous sent to Microbiology. After all cultures were proven negative, 48 hours after presentation and after minimal improvement on antibiotic therapy, a revised diagnosis of likely immune-related adverse event in response to pembrolizumab was made. Antibiotics were discontinued, and oral prednisolone at a dose of 1mg/kg was commenced, alongside topical steroid and atropine eye drops. Within one week of starting steroid treatment, the left eye pain, eyelid swelling and conjunctival chemosis has subsided completely (Figure 3). The anterior chamber fibrinous inflammatory reaction had lessened, and the haemorrhagic vitreous opacity was showing consolidation. However, the patient's visual acuity in the left eye remains at no perception of light. Pembrolizumab treatment has been discontinued, and the patient remains on best supportive care.

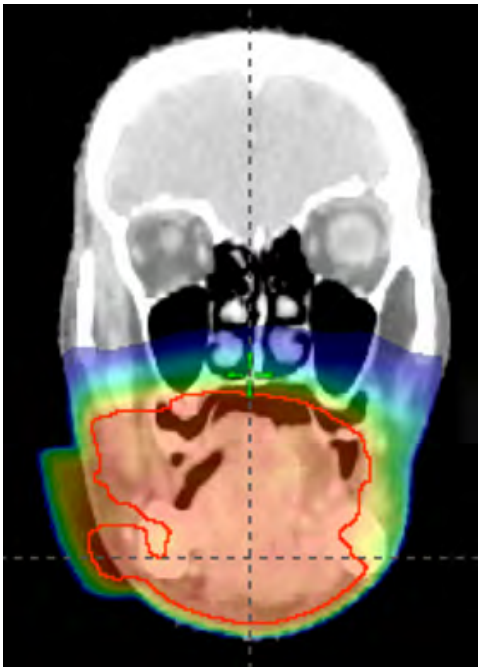

Figure 1: Colour wash of radiotherapy plan, showing prescribed volume (36Gy) in red and low dose (5Gy) in blue. The eyes received no dose of radiotherapy.

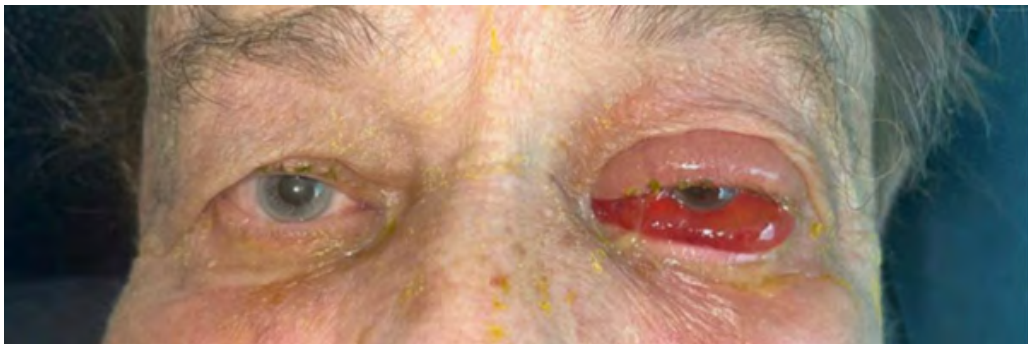

Figure 2: Left eyelid swelling, conjunctival chemosis and injection on initial presentation.

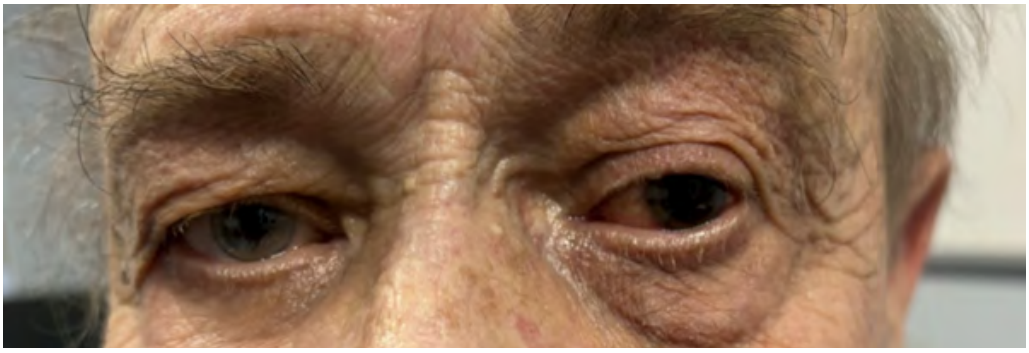

Figure 3: Complete resolution of left eyelid swelling and conjunctival cheimosis 6 days after commencement of oral steroid therapy.

4. Discussion

Pembrolizumab is a relatively recent addition to the armoury used against metastatic and unresectable recurrence of head and neck squamous cell carcinoma. As an immune checkpoint inhibitor targeting the programmed cell death (PD-1) protein on T cells, it is able to block the downregulation of the adaptive immune system and augment the attack on tumour cells. However, this disruption of usual immune regulation has led to increasing reports of immune-related adverse events associated with pembrolizumab, as well as other immune checkpoint inhibitors [4]. Ocular immune-related adverse events comprise a small proportion of these adverse events, and remain poorly characterised, yet can have wide-ranging and potentially sight-threatening effects. Martens *et al.* (2023) [5] categorise these ocular adverse events into (i) uveitis, (ii) neuro-ophthalmic (myaesthaenia gravis, optic nerve or other cranial nerve disorders), (iii) orbital disorders (orbital inflammation, myopathy), (iv) retinal dysfunction, and (v) ocular surface disorders (dry eye disease, blepharitis, conjunctivitis, episcleritis, scleritis, keratitis).

The most common ocular immune-related adverse event associated with pembrolizumab is uveitis, with pembrolizumab-associated panuveitis (as in our case) representing 50% of all reported immune checkpoint inhibitor-related panuveitis in the literature [6]. Overall incidence of panuveitis related to pembrolizumab remains low however, with thirteen reports to date. Of note, the shortest time between initiation of immune checkpoint inhibitor treatment and onset of uveitis previously reported is two weeks (with longest latency two years) [5]. To our knowledge, this case represents the first report of panuveitis associated with pembrolizumab infusion occurring within three days of first treatment. Interestingly, the cases of immune checkpoint inhibitor-related panuveitis reported to date indicate a promising response to steroid treatment, with Chaudot *et al.* (2022) [6] reporting 81% patients achieving partial or complete response to treatment. Similarly, Telfah *et al.* (2019) [7] report return of vision to baseline after discontinuation of immunotherapy treatment and commencement of systemic and topical steroid treatment. Unfortunately, the same was not true of our case, whose sight loss remained despite his periocular pain and inflammation responding well to steroids. This may reflect a mixed picture of optic neuropathy in addition to severe inflammation responsible for sight loss in our case. Such acute-onset sight loss with panuveitis occurring after the first dose of pembrolizumab infusion, though representing the first reported case to date, holds implications for pre-treatment counselling and post-treatment monitoring. Though many ocular immune-related adverse events are mild and do not necessitate discontinuation of therapy [8], prompt recognition of severe ocular symptoms, by both patients and healthcare professionals, and appropriate multi-disciplinary liaison between oncology and ophthalmology may allow for earlier initiation of treatment and prevention of sight loss [9].

5. Learning Points

- Immune checkpoint inhibitors such as pembrolizumab may result in severe ocular inflammation and sight loss. Both physicians and patients need to be aware of this rare, but serious, risk.

In patients receiving cancer immunotherapy and presenting with ocular symptoms, a multi-disciplinary approach between oncology and ophthalmology can allow for early identification of immune-related adverse events and initiation of treatment.

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