Immune Checkpoint Inhibitors-Associated Optic Neuritis: The First Reported Case induced by Cemiplimab and a Review of the Literature

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BACKGROUND **Immune checkpoint inhibitors (ICIs)** are a class of monoclonal antibodies increasingly employed in the treatment of malignancies to **enhance T-cell-mediated antitumor immunity**. **Despite their efficacy, ICIs may elicit immune-related adverse events**, including rare, yet potentially vision-threatening, optic neuritis.

AIMS To report **the first case of optic neuritis associated with Cemiplimab** (PD-1 inhibitor) and provide a **focused literature review on ICI-induced ON**.

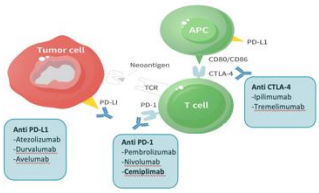

Fig. 1 *ICIs' molecular mechanism of action*

METHODS A systematic PubMed search was conducted. A total of 15 case reports and one case series (10 patients) were included, for a combined cohort of 25 prior patients since 2015. Data were analysed descriptively.

CASE REPORT a 74-year-old Argentinian male developed **sudden, painless visual loss in OS**. Ophthalmologic evaluation revealed a **central scotoma and optic disc oedema**. Orbital MRI showed T2 hyperintensity of the left optic nerve. CSF analysis documented lymphocytic pleocytosis hyperproteinorrachia. Extensive infectious and autoimmune work-up was negative. **Cemiplimab was discontinued,** and a **5 days-IVMP-cycle was administered**. One month later, the patient showed **resolution of visual symptoms** with partial resolution of oedema and **mild optic disc pallor**. *However*, 18F-FDG PET/CT scan revealed focal radiotracer uptake in the right lung and in bilateral paratracheal and hilar lymph nodes, as well as in the left adrenal gland, suggesting **cancer progression.**

RESULTS Among the 25 patients (39 affected eyes) reviewed mean age was 57.2 (SD 15.0), and 55% were male. All ICIs were implicated though **anti PD-1 were the most frequently involved** (64% as monotherapy and 28% in combination) (Fig 2). **Mean ICIs cycles before ON onset was 6.4** (SD 9.9) though only two patients had received more than 10 cycles. The most frequent underlying malignancy was **cutaneous melanoma** (36%, n=9).

Acute visual acuity reduction was ON presenting symptom in 24 patients. A single ON was an incidental finding. Visual field testing was performed in 19 out of 25 patients. Among the 16 cases with abnormal CVF, 6 exhibited a cecocentral defect, 5 had altitudinal defects and in 4 the defect was diffuse.

ICIs were discontinued in 80% (n=20, non colored boxes in Tab. 1). Acute IV steroids were administered in 72%, with escalation to second-line tp (IVIG/PLEX) in 12%. Oral steroid tapering was completed in 68%. Maintenance immunosuppression was initiated in 16% (4), including RTX in the two anti AQP-4 positive patients.

Acute treatment	Chronic treatment	Outcome	Acute treatment	Chronic treatment	Outcome
IV steroids for 5 days	Oral steroids tapering	BVCA: Partial recovery (OD 20/200) Fundus: Not assessed	IV steroids for 5 days	Oral steroids tapering	BVCA: Not assessed Fundus: Disc pallor
IV steroids for 5 days	Oral steroids tapering - RTX	BVCA: Partial recovery (OS 20/30) Fundus: Not assessed	IV steroids for 5 days	Oral steroids tapering for 6 mo	BVCA: Partial recovery Fundus: Not assessed
IV steroids for 5 days	Oral steroids tapering for 10 weeks - RTX	BVCA: Full recovery Fundus: Not assessed	Topical steroids	*no chronic treatment*	BVCA: Partial recovery Fundus: Full recovery
IV steroids for 5 days	*no chronic treatment*	BVCA: Unchanged; Relapse Fundus: Not assessed	IV steroids for 5 days	Oral steroids tapering	BVCA: Partial recovery Fundus: Partial recovery
IV steroids for 5 days	Oral steroids tapering for 1 mo	BVCA: unknown Fundus: Disc pallor	IV steroids for 5 days	Oral steroids tapering	BVCA: Unchanged Fundus: Partial recovery
no acute treatment	Oral steroids with tapering	BVCA: unknown Fundus: Disc pallor	*No treatment*	*No treatment*	BVCA: Partial recovery; full recovery Fundus: Partial recovery; partial recovery
IV steroids for 3 days - IVIG -PLEX	Oral steroids tapering for 3 mo	BVCA: Not assessed Fundus: Disc pallor	IV steroids for 5 days; IV steroids for 5 days - IVIG - PLEX	Mycophenolate mofetile for 6 mo	BVCA: Partial recovery Fundus: Not assessed
Oral steroids	Oral steroids tapering	BVCA: Not assessed Fundus: Disc pallor	IV steroids for 3 days	*no chronic treatment*	BVCA: Partial recovery Fundus: Disc pallor
IV steroids for 5 days	Oral steroids tapering for 2 mo	BVCA: Not assessed Fundus: Full recovery	IV steroids - IVIG	Infliximab	BVCA: Partial recovery Fundus: Not assessed
Oral steroids	Oral steroids tapering	BVCA: Not assessed Fundus: Disc pallor	IV steroids for 5 days	*no chronic treatment*	BVCA: Partial recovery; full recovery Fundus: Not assessed
IV steroids for 3 days	Oral steroids tapering for 2 mo	BVCA: Not assessed Fundus: Disc pallor	IV steroids for 3 days	Oral steroids tapering - Mycophenolate mofetil for 6 mo	BVCA: Unchanged Fundus: Not assessed
IV steroids for 3 days	Oral steroids tapering	BVCA: Not assessed Fundus: Partial recovery	Oral steroids	Oral steroids tapering	BVCA: Unchanged Fundus: Not assessed
No treatment	*No treatment*	BVCA: Not assessed Fundus: Disc pallor	*IV steroids for 5 days*	*no chronic treatment*	*BVCA: Full recovery Funds: Disc pallor*

Tab. 1 *Therapeutic management and ophthalmologic outcomes in reported ICIs-induced ON*

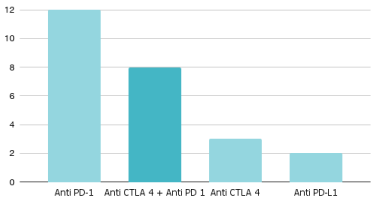

Fig. 2 *Distribution ICIs classes in reported ICIs-induced ON*

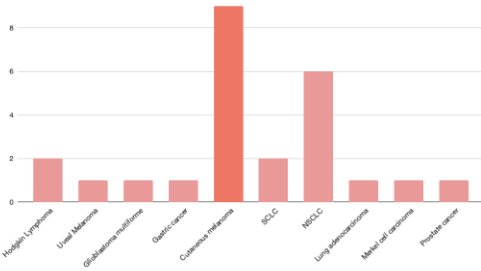

Fig. 3 *Distribution of underlying malignancies in reported ICIs-induced ON*

KEY FINDINGS

Clinical presentation diverged from typical ON

as 56% were bilateral, 80% painless and 84% with preserved color vision.

Preferential anterior involvement

Fundus oculi, performed in 22 patients, showed **prominent disc oedema in 90.91% of the tested** (20). Among the 22 patients who underwent **orbital MRI, 54.55% showed no signal abnormalities of the optic nerve.** CNS lesions were observed in 2 patients (1 with four brain lesions, 1 with LETM), both AQP-4 + (the only 2 positives, among the 7 tested).

Unmatched therapeutic need

Only two case report explicated long-term cancer outcomes, and in both cases tumor progression led to exitus. This highlights the urgent need to develop targeted strategies against ir-AEs without compromising cancer control.