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Optic neuropathies induced by immune checkpoint inhibitors: A case series and systematic review of the literature

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ABSTRACT

Introduction: Immune checkpoint inhibitor (ICI)-related optic neuritis is rare but clinically significant as visual sequelae are reported in around half of affected patients.
Materials and methods: We retrospectively collected all cases of ICI-related optic neuropathy referred to two tertiary centers. A systematic review of PubMed, Embase, and Medline was conducted following PRISMA guidelines. Cases were classified into: i) optic neuritis, defined by the presence of consistent symptoms (visual loss, dyschromatopsia, afferent pupillary defect) and optic nerve abnormalities on MRI or visual evoked potentials (VEPs); ii) papillitis, defined by any visual disturbance associated with optic disc oedema and absence of optic neuropathy signs on MRI imaging or VEPs.
Results: Fifty cases were identified. The most common presentation was bilateral, painless visual acuity reduction with papilledema. All optic neuritis cases involved vision loss compared to 60 % of papillitis patients, who also reported scotomas, photopsia, or floaters. Papillitis was frequently associated with uveitis, either isolated or as part of Vogt-Koyanagi-Harada-like syndrome, whereas optic neuritis was more often associated with immune-related neurological toxicities, including neuromyelitis optica spectrum disorder.
Despite immunomodulatory treatment, visual deficits persisted in 60 % of cases – rising to nearly 80 % in optic neuritis cases. Seven patients with papillitis and one with optic neuropathy resumed ICIs without recurrence.
Conclusions: Two distinct patterns of ICI-induced optic neuropathy emerge: papillitis, usually associated with uveitis and Vogt-Koyanagi-Harada syndrome, and optic neuritis, linked to broader immune-related neurological toxicities and poorer outcomes. Our findings suggest that ICIs may be safely reintroduced after full recovery from ICI-related papillitis.

Abbreviations: CcRCC, Clear cell renal cell carcinoma; CSF, Cerebrospinal fluid; CTLA-4, Cytotoxic T-lymphocyte associated antigen-4; ICI, Immune checkpoint inhibitor; IrAEs, Immune-related adverse events; IrON, Immune-related optic neuritis; IVIG, Intravenous immunoglobulin; MOG, Myelin oligodendrocyte glycoprotein; NMOSD, Neuromyelitis optica spectrum disorder; NSCLC, Non small cell lung cancer; OCT, Optic coherence tomography; PD-1, Programmed cell death 1; PDL1, Programmed cell death ligand 1; SCLC, Small cell lung cancer; VEPs, Visual evoked potentials; VKH, Vogt-Koyanagi-Harada.

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1. Introduction

Immune checkpoint inhibitors (ICIs) have revolutionized cancer therapy by restoring antitumor immunity through blockade of inhibitory T cell pathways, notably CTLA-4 and PD-1. While these monoclonal antibodies effectively reactivate tumor-reactive T cells, they also disrupt immune homeostasis, leading to immune-related adverse events (irAEs) that most commonly affect the gastrointestinal tract, lungs, skin, liver, and endocrine system [1–4].

Ocular irAEs are rare, occurring in only 2–4 % of ICI-treated patients and typically manifest as myasthenia-like ophthalmoplegia, uveitis, or dry eye [5, 6]. Optic neuropathy, though accounting for just 4 % of ocular irAEs, carries significant clinical weight due to its potential for persistent visual impairment in up to half of affected patients [5, 7]. Diagnostic criteria for ICI-related optic neuritis have been proposed, requiring consistent symptoms (visual loss, dyschromatopsia, afferent pupillary defect) alongside optic nerve abnormalities on MRI consistent with acute demyelination (contrast enhancement and/or T2 hyperintensity) and clinical improvement or stabilization following immunomodulating therapy (including steroids) or ICI discontinuation [8]. However, many reported cases fail to meet these criteria, and the direct application of diagnostic frameworks derived from idiopathic optic neuritis may not be appropriate for ICI-induced cases. This challenge mirrors that observed in other ICI-associated neurological syndromes, such as Guillain-Barré-like syndrome, which exhibits distinct clinical and therapeutic features compared to its classic form [9]. Therefore, a detailed characterization of the clinical syndrome is of paramount importance to guide clinicians in accurate diagnosis and management.

In this study, we present the combined experience of two referral centers alongside a systematic review of the literature on immune-related optic neuropathies, with the aim of characterizing their clinical features, outcomes, and the tolerability of ICI reintroduction following toxicity.

2. Materials and methods

2.1. Patient selection

We report a retrospective series of patients with an ICI-related optic neuritis, referred between January 2018 and June 2025 to two tertiary centers: Saint Louis/Lariboisière hospital, Paris, France and Azienda Sanitaria Universitaria Friuli Centrale (ASUFC), Udine, Italy. Other causes of optic neuropathy were excluded by blood analysis and brain MRI. Melanoma patients were registered in MelBase, a French clinical database with a biobank of adult melanoma patients that was approved by the French ethics committee (CPP Ile-de-France XI, n°12027, 2012) and registered in the NIH clinical trials database (NCT02828202). The study was also approved by the Regional ethics committee of the Friuli Venezia Giulia Region, Italy (Ref. No. CEUR-2023-Os-102 “Neuro-Checkmate”). Written informed consent was obtained from all patients.

2.2. Systematic review

The systematic review was conducted in accordance with the Preferred Items for Systematic Review and Meta-analyses (PRISMA). Details of the protocol for this systematic review were registered on PROSPERO and can be accessed at https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42024591659. A comprehensive literature search on the PubMed, Embase and Medline databases was performed on September 17, 2024. The detailed search strategy is attached as supplementary data (S1). Covidence was used to manage the records identified by the literature search. Each study was screened by two reviewers (SC and EL) independently, for title and abstract, and then for full text. A manual snowballing search from selected studies was also conducted by EL. Figure 2 shows the flowchart of the systematic search and selection process. All articles reporting at least one case of optic neuropathy following ICI treatment were included. Cases with non-comprehensive descriptions or causes of neuropathy other than ICIs were excluded. Data were extracted for each included case, comprising patient demographics (age, sex, cancer type), intervention (ICI, cycles, and duration), clinical features (symptoms, results of radiologic, biological and electrodiagnostic studies), treatment and outcome.

2.3. Classification of patients

On the basis of these features, we identified the cases of optic nerve damage related to ICIs and distinguished two patterns: optic neuritis and papillitis. Optic neuritis was defined by the presence of both consistent symptoms (visual loss, dyschromatopsia, afferent pupillary defect) and evident optic nerve abnormalities on MRI imaging (contrast enhancement and/or T2 hyperintensity) or on visual evoked potentials (VEPs) (axonal or demyelinating neuropathy). Papillitis was defined by the presence of any visual disturbance, including scotomas or altered color vision, associated with optic disc edema at fundus examination and the absence of signs of optic neuropathy on MRI imaging and VEPs.

2.4. Statistical tests

Categorical variables were compared between the papillitis and optic neuritis groups using the χ^2 test or Fisher’s exact test, as appropriate. For multiple comparisons, p-values were adjusted using the Bonferroni correction. Statistical significance was set at $p < 0.05$ for global comparisons and at $p < 0.0083$ for individual symptom/toxicity analyses (after Bonferroni adjustment). All analyses were performed using R software (version 4.2.0).

3. Results

3.1. Original case series

We identified seven patients who developed an ICI-related optic neuropathy in the study period, three with ir-papillitis (Table 1) and four with ir-optic neuritis (Table 2). None of the patients had a known history of pre-existing autoimmune disease.

In the overall cohort, symptoms occurred after a median delay of 20 weeks from ICI initiation. Patients with optic neuritis presented with unilateral or bilateral visual acuity reduction, while those with papillitis reported scotomas; notably, none experienced eye pain. Ophthalmological examination revealed bilateral papilledema in all patients with papillitis and in 2 of 4 patients (50 %) with optic neuritis, confirmed by fundus fluorescein angiography and optic coherence tomography (OCT) (Figure 1). Visual evoked potential (VEPs) confirmed a bilateral involvement of the optic nerves in all optic neuritis patients. Brain MRI, performed in all patients, showed contrast enhancement (right optic nerve) only in one patient (Patient #7).

Among the three papillitis cases, ICIs were discontinued in only one patient (Patient #2) due to ocular toxicity. In this patient, ICIs were successfully reintroduced after 4 months and continued for 2 years, with no recurrence of papillitis observed at the 7-year follow-up.

In Patient #1, ICIs were continued with the same regimen and without steroids, while in Patient #3, ICIs were stopped due to other immune-related toxicities (meningitis, hepatitis, colitis), precluding reintroduction. All three patients achieved complete symptom and sign resolution during ophthalmological follow-up.

Among the four patients with optic neuritis, three received steroid treatment. Only Patient #4 experienced complete recovery, while two others had a persistent severe visual acuity impairment despite treatment with IV methylprednisolone or a combination of IV methylprednisolone, IVIG and tocilizumab, respectively. The other case (Patient #5) experienced visual improvement despite continued ICI treatment.

Table 1
Characteristics of the patients with ir-papillitis in our centers.

Case	Age (years)	Malignancy	ICIs	Time to symptoms (weeks)	Symptoms	Fundus examination	Intraocular inflammation	Other non-ocular toxicity	Treatment	Ocular outcome	ICI continuation / reintroduction?	Ocular follow up
#1	64	Melanoma	Ipilimumab + Nivolumab	28	Photopsia OD	Bilateral optic disc edema	No	None	None	Complete recovery	Continuation	No recurrence of papillitis
#2	55	Melanoma	Ipilimumab + Nivolumab	16	Bilateral colorful scotomas	Bilateral optic disc edema	No	Hypophisitis	None	Complete recovery	Reintroduction (Nivolumab)	No recurrence of papillitis
#3	45	Melanoma	Ipilimumab + Nivolumab	20	Black scotoma OD	Bilateral optic disc edema	Uveitis	Vitiligo, meningitis, hepatitis, hypoacousia (VKH) colitis	Prednisone given because of other ir-AEs	Complete recovery	No (due to other ir-Aes)	No recurrence of papillitis

VA: visual acuity, OD: right eye

Table 2
Characteristics of the patients with ir-optic neuritis in our centers.

Case	Age (years)	Malignancy	ICIs	Time to symptoms (weeks)	Symptoms	Fundus examination	Intraocular inflammation	Non-ocular toxicity	Treatment	Ocular outcome	ICI continuation / reintroduction?	Ocular follow up
#4	52	Melanoma	Pembrolizumab	6	Bilateral VA reduction	Bilateral optic disc edema	Panuveitis	Vitiligo	Prednisone	Complete recovery	No	Normal
#5	79	Squamous-cell carcinoma	Cemiplimab	12	VA reduction OD	Bilateral optic disc edema	No	Thyroiditis, Hepatitis	None	Partial recovery	Continuation	Stable
#6	58	Melanoma	Pembrolizumab	20	VA reduction OS (hand motion	Normal	No	Thyroiditis	Methylprednisolone	Stable	No	Stable
#7	54	Clear renal cell carcinoma	Pembrolizumab	28	VA reduction OD (hand motion)	Normal	No	CNS demyelinating lesions, myositis, hepatitis, skin rash, colitis	Methylprednisolone, prolonged steroid taperig, IVIG, tocilizumab	Stable	No	Stable

CNS: central nervous system, VA: visual acuity, OD: right eye, OS: left eye

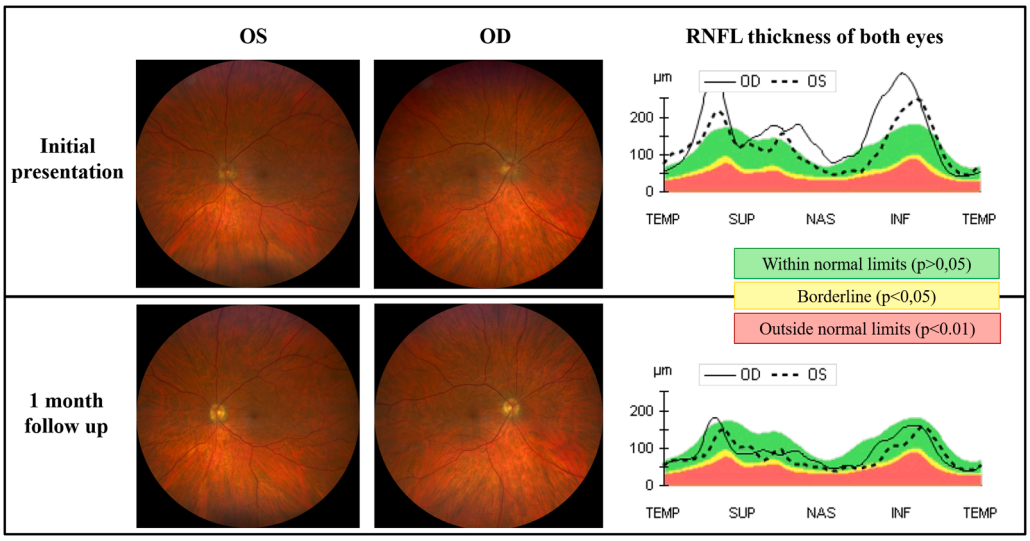

Fig. 1. Ophthalmological examination of Patient #1 of the original case series. Bilateral color retinophotography and papillary optical coherence tomography at initial presentation (upper part), showing the blurry boarders of the optic disc with and increased thickness of the retinal nerve fiber layer, suggesting bilateral papilledema, which spontaneously regressed at one month follow-up (bottom part).

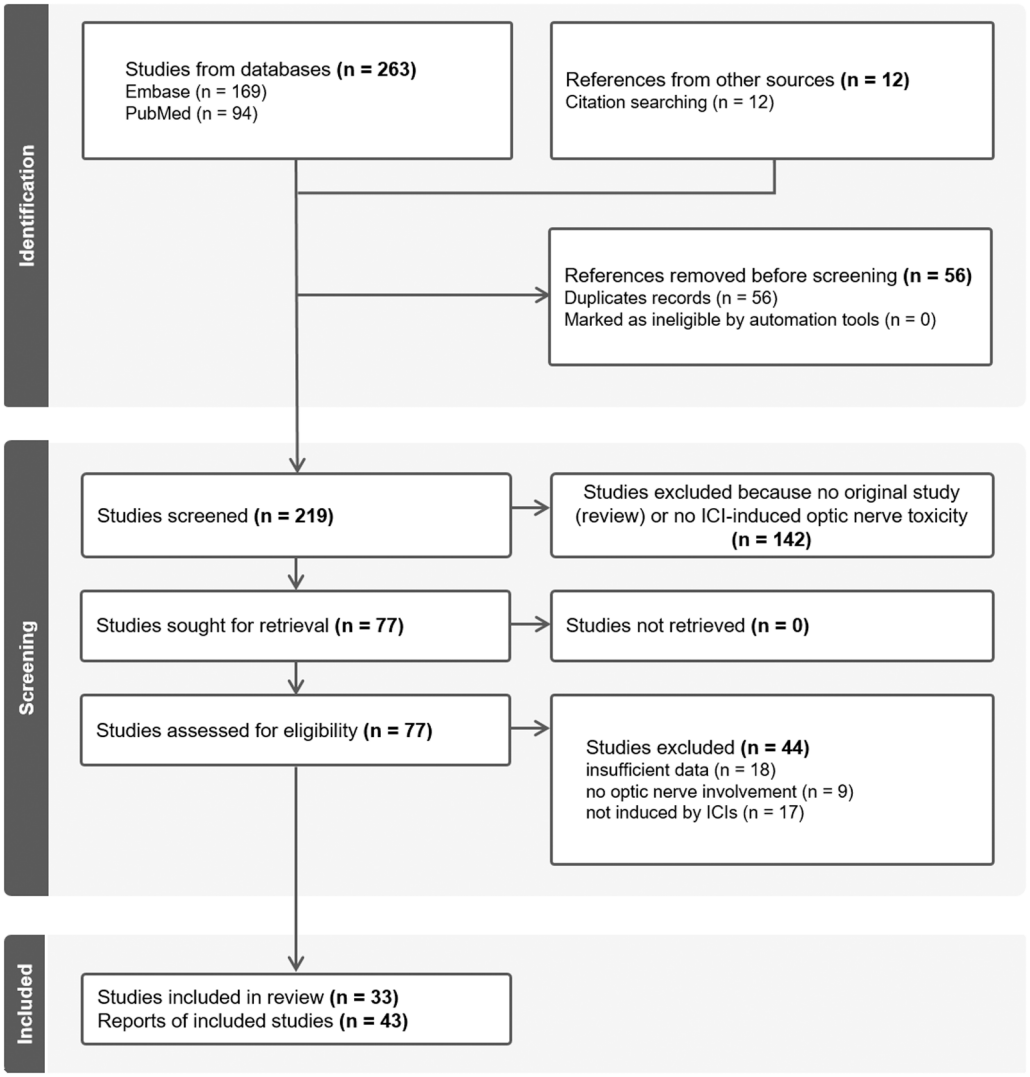

Fig. 2. PRISMA flow diagram of selection strategy for the systematic review of the literature.

3.2. Systematic review of the literature

To assess the relevance of our findings, we conducted a systematic review of the literature on optic neuropathies associated with ICIs. A total of 33 studies were included, comprising 43 cases analyzed in this review. The search strategy is presented in Figure 2.

Median time from the initiation of the immunotherapy to the onset of visual disturbance was 12 weeks after a median of four ICI doses. No difference in timing of onset and doses administered was found between patients developing papillitis and those with optic neuritis.

The clinical features are summarized in Table 3, and a detailed description of these cases is attached as supplementary data (Tables S1-S4). In all reported cases, no pre-existing autoimmune disease was mentioned. Compared to papillitis, optic neuritis was less frequently associated with uveitis and Vogt-Koyanagi-Harada (VKH) syndrome but more commonly linked to other neurological ir-toxicities. Notably, two patients classified as papillitis also presented with ir-neurotoxicities, yet without other signs of VKH syndrome. However, diagnostic uncertainty persists in these cases: one patient underwent brain MRI only, and the other had neither MRI nor visual evoked potentials (VEPs) performed, precluding the exclusion of extensive optic neuritis (Patients P3, P25 [10, 11] (Tables 3, S1).

AQP4-directed antibodies were found in the serum of two patients with ir-optic neuritis. Patient ON16 developed a rare NMSOD associating optic neuritis, myelitis and diencephalic involvement, whereas patient ON17 patient experienced unilateral optic neuritis presenting with vision loss and pain with eye movement, thus recalling the clinical pattern of non-ICI-related optic neuritis [12, 13]. The authors reported no ocular or neurological symptoms in either patient prior to ICI treatment. The other patient with NMOSD (ON10) was negative for both anti MOG and AQP4 antibodies [14].

Among published cases, five patients with papillitis and one wit optic neuropathy were successfully rechallenged with ICI therapy following recovery from the initial adverse event; none of them experienced recurrent optic toxicity (Tables S2 and S4). However, in 3 cases of papillitis, uveitis recurred upon ICI reintroduction.

Table 3
Characteristics of the patients from the systematic review of the literature.

	Papillitis (n = 25)	Optic neuritis (n = 18)
Symptoms*	Decreased / blurry vision (17/25, 70 %) Floaters (5/20, 25 %) Pain associated with uveitis (5/20, 25 %) Photopsia (2/20, 10 %) Central scotoma (1/20, 5 %) Dyschromatopsia (1/20, 5 %)	Decreased / blurry vision (100 %) Floaters (1/18, 6 %) Dyschromatopsia (1/18, 6 %) Pain with eye movement (1/18, 6 %)
Bilateral involvement	20/25 (80 %)	15/18 (83 %)
Association with uveitis	17/24 (71 %)	2/18 (11 %)
Association with neurological ir-toxicities**	6/24 (25 %) (VKH-like syndromes)	6/18 (33 %)
Anti MOG antibodies	0/1 (0)	0/8 (0)
Anti QP4 antibodies	0/1 (0)	2/8 (25 %)
Treatment	Systemic steroids (15/25, 60 %) Topical steroids (3/25, 12 %) Systemic steroids + IVIG (1/25, 4 %) Systemic steroids + infliximab (1/25, 4 %) Systemic steroids + IVIG + infliximab (1/25, 4 %) Systemic steroids + plasma exchange + rituximab (1/25, 4 %) Systemic steroids + mycophenolate mofetil + methotrexate (1/25, 4 %) No treatment (8 %)	Steroids (8/18, 44 %) Steroids + plasma exchange (4/18, 22 %) Steroids + plasma exchange + IVIG + mycophenolate mofetil (2/18, 11 %) Steroids + plasma exchange + rituximab (2/18, 11 %) Steroids + IVIG (1/18, 6 %) No treatment (1/18, 6 %)
ICI reintroduction	5/25 (20 %)	1/18 (6 %)
Toxicity recurrence	3/5 (60 %): uveitis but not papillitis recurrence	0/1 (0)

*Percentage of patients presenting the mentioned symptoms, more than one symptom can be present in the same patient.
**VKH (Vogt-Koyanagi-Harada) syndrome included: lymphocytic meningitis (n = 2), sensorineural hearing loss (n = 2), vitiligo (n = 3) and poliosis (n = 2). In patients with papillitis, other reported neurotoxicities included: sensory neuronopathy (n = 1), peripheral neuropathy not better specified (n = 1), meningomyelitis (n = 1). In the optic neuritis group, neurotoxicities comprised meningitis (n = 2), meningoradiculitis (n = 1), myelitis within the NMOSD (n = 2), other cranial nerve involvement (n = 1).
Cases with no data about the specific characteristic are excluded from the percentages.

3.3. Overall analysis of the original cohort and cases from the review of the literature

We analyzed the whole cohort of 50 patients (43 from the review of the literature and 7 from our centers) to validate the specific patterns of ir-papillitis (n = 28) and ir-optic neuritis (n = 22). With regard to malignancy, patients with papillitis were more commonly affected by melanoma than those with optic neuritis (64 % versus 45 %) although this difference was not significant. Optic neuropathies are reported with both anti-CTLA4 and anti-PD1, as monotherapies or combination of them. Anti-PD1 and especially pembrolizumab seems associated with a greater likelihood of these toxicities, however this result could depend on the larger use of pembrolizumab and nivolumab in clinical practice. No specific association was found between ocular toxicity and ICI class or agent (Figure 3). In both groups, the most common pattern consisted of painless reduction of visual acuity and bilateral papilledema. However, clinical presentation differed significantly between the two groups with papillitis or optic neuritis ($p < 0.0001$, χ^2 test). Whereas decreased vision was universally present in the optic neuritis group (22/22), only 60 % of patients with ir-papillitis experienced blurry or decreased vision (17/28) ($p = 0.0002$, Fisher's exact test). Other symptoms, such as floaters, photopsia, floaters and pain related to uveitis, showed non-significant trends towards higher frequency in the papillitis group (Figure 4A).

In addition, the distribution of associated toxicities differed significantly between the papillitis and optic neuritis groups ($p = 0.0012$, χ^2 test). Compared to optic neuritis, papillitis was mainly distinguished by its association with uveitis (67 %) either isolated or in the context of a Vogt-Koyanagi-Harada-like syndrome ($p = 0.004$, Fisher's exact test), while ir-neurotoxicity without uveitis showed a non-significant trend towards higher frequency in the optic neuritis group (6/22 vs 2/28, $p = 0.04$) (Figure 4B).

Overall, most patients with either papillitis or optic neuritis were treated with steroids alone or in combination with other immunomodulatory therapies (Figure 4C). In the papillitis group, systemic steroid therapy primarily consisted of oral steroids (60 % of cases), with prednisone at 1mg/Kg/day being the most frequently administered regimen. This was followed by a gradual tapering over several weeks. For patients receiving IV steroids, the dosage and duration varied significantly - ranging from methylprednisolone at 1 mg/kg/day to 1000 mg/day - though all cases included a subsequent tapering phase with oral prednisone. In the optic neuritis group, oral prednisone (1 mg/Kg with gradual tapering over several weeks) was used in only three cases. The majority of patients received high-dose IV steroids for 3–5 days, either followed (n = 9) or not followed (n = 6) by oral prednisone tapering over several months. IV steroid doses ranged from 125 mg/day to 1000 mg/day.

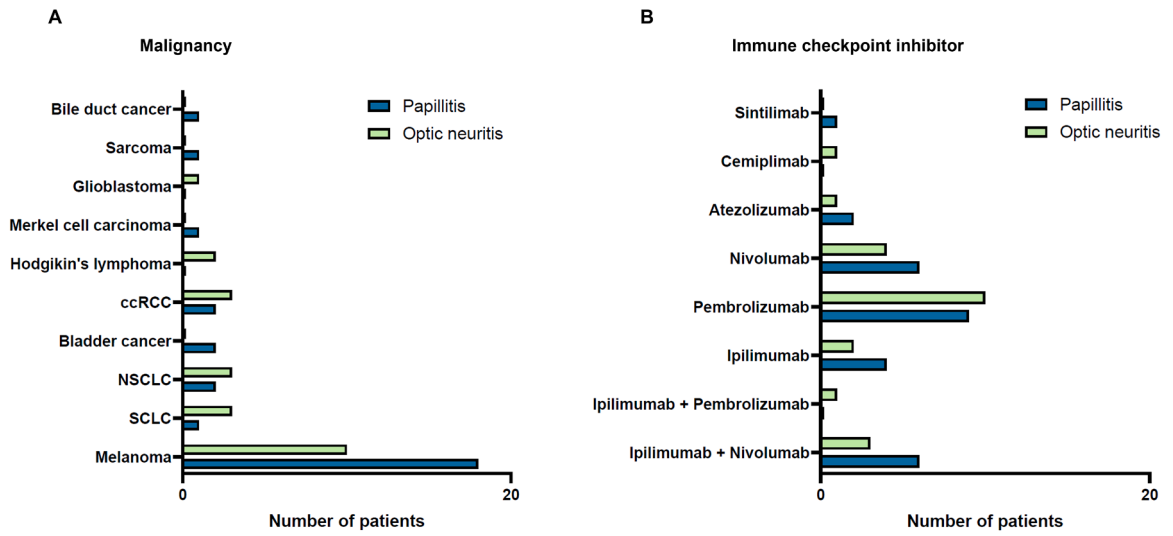

Fig. 3. Cancer characteristics of the patients developing an optic neuropathy associated with ICIs. Distribution of cancer type (A) and of ICI regimen (B) in the two groups of patients with ir-papillitis (n = 28) and ir-optic neuritis (n = 22) among the whole cohort (n = 50). SCLC: small cell lung cancer, ccRCC: clear cell renal cell carcinoma, NSCLC: non-small cells lung cancer.

As expected, the outcome was poorer in patients with optic neuritis, with visual deficits persisting in 77 % of patients (compared to 41 % of patients with ir-papillitis) (Figure 4D). No significant association was observed between steroid dosage or treatment duration and clinical outcome. The interval between symptom onset and steroid initiation was not consistently reported in published cases. However, in most cases of optic neuritis, authors noted that systemic steroids were administered promptly following diagnosis. In contrast, five cases of papillitis described a delay in systemic steroid administration, with initial treatment limited to topical steroids. Given the paucity of detailed data, the potential impact of delayed steroid therapy on the clinical outcomes of immune-related optic neuropathies remains unclear.

4. Discussion

Our case series, combined with a systematic literature review suggests that the extent of optic nerve involvement distinguishes two distinct clinical patterns: papillitis and optic neuritis. Consistent with previous reports [6, 15], the most common presentation of ICI-related optic nerve disorder is bilateral painless visual loss with papilledema. However, inflammation is confined to the optic disc (papillitis), other intraocular inflammations - particularly uveitis - is frequently observed (67 % of cases). Interestingly, nearly one third of these patients also exhibited features of a Vogt-Koyanagi-Harada (VKH)-like syndrome, including generalized anhidrosis, vitiligo, poliosis, lymphocytic meningitis, hypophysitis, and sensorineural hearing loss. In addition, eight cases (P2, P5, P13, P10, P15, P16, P17, and P20) developed posterior uveitis with stromal choroiditis and retinal vasculitis, mimicking autoimmune Birdshot uveitis (Table S1).

VKH is a CD4 + T-cell-mediated autoimmune condition targeting melanocytes [16]. Therefore, it is not surprising that VKH-like syndromes are relatively common in melanoma patients treated with ICIs, as these agents may stimulate immune responses not only against melanoma cells but also against normal melanin-containing tissues [15, 17]. The frequent occurrence of VKH-like syndromes and Birdshot-like uveitis in this population further supports a T-cell-mediated pathophysiology of these immune-related adverse events.

In contrast to idiopathic optic neuritis, ICI-related optic neuritis is characterized by bilateral nerve involvement and visual acuity loss, while color vision is usually unaffected (only one case in our series). While ir-papillitis is often associated with intraocular inflammation, ir-optic neuritis is more frequently associated with neurological toxicities such as meningitis, meningoradiculitis, myelitis as NMOSD and other cranial nerve involvement.

The leading pathophysiological hypothesis for ir-optic neuritis involves a T-cell-mediated attack on the optic nerve, supported by the frequent detection of inflammatory CSF and a favorable response to corticosteroids [7]. However, paraneoplastic mechanisms cannot be ruled out: paraneoplastic NMOSD has been described in association with various cancers [18], and two patients in our review tested positive for anti-AQP4 antibodies. As for other paraneoplastic syndromes, few reports have described some patients with recrudescence of MOGAD (Myelin oligodendrocyte glycoprotein antibody-associated disease) symptoms after ICIs [19, 20]. Although it is not often known whether these antibodies pre-existed prior to ICI treatment, it seems logical that immune checkpoint blockade may trigger or exacerbate pre-existing autoimmune responses, as described in some cases of ICI-related encephalitis with neural autoantibodies [21]. In light of the studies on non-ICI related NMSODs, T-cell responses may also play a key role in the development of AQP4 + NMOSD after ICI. Indeed, T-cell responses to AQP4 and T17 deviation have been shown in patients with AQP4 + NMOSD [22]. In addition, in one of the two cases in this review (case ON16, lung adenocarcinoma), immunohistochemistry of the lung biopsy specimens suggested that pulmonary AQP4 antigen was scavenged by local macrophages, suggesting antigen presentation to T-cells.

From a clinical perspective, the two AQP4 + patients exhibited distinct patterns compared to the other patients of the series: ON16 developed NMOSD associating optic neuritis, myelitis and diencephalic involvement, while ON17 presented with unilateral painful optic neuritis, thus resembling non-ICI-related optic neuritis [12, 13]). Of note, another patient developed NMOSD (ON10) but tested negative for both anti-MOG and-AQP4 antibodies [14]. No patient tested positive for anti MOG antibodies.

Unlike idiopathic forms, most patients included in our systematic review did not recover full vision despite treatment with corticosteroids and other immunomodulatory therapies such as IVIG, plasma exchange, infliximab, rituximab, and mycophenolate mofetil. This poor outcome was particularly evident in optic neuritis (78 %), but half of the papillitis patients also failed to achieve complete recovery. The four patients with NMSOD (with or without AQP4 antibodies) experienced a partial or complete recovery of symptoms and radiologic features.

Given this poor outcome, only a few cases of rechallenge with ICIs after an immune-related papillitis and only one after ir-optic neuritis have been reported.

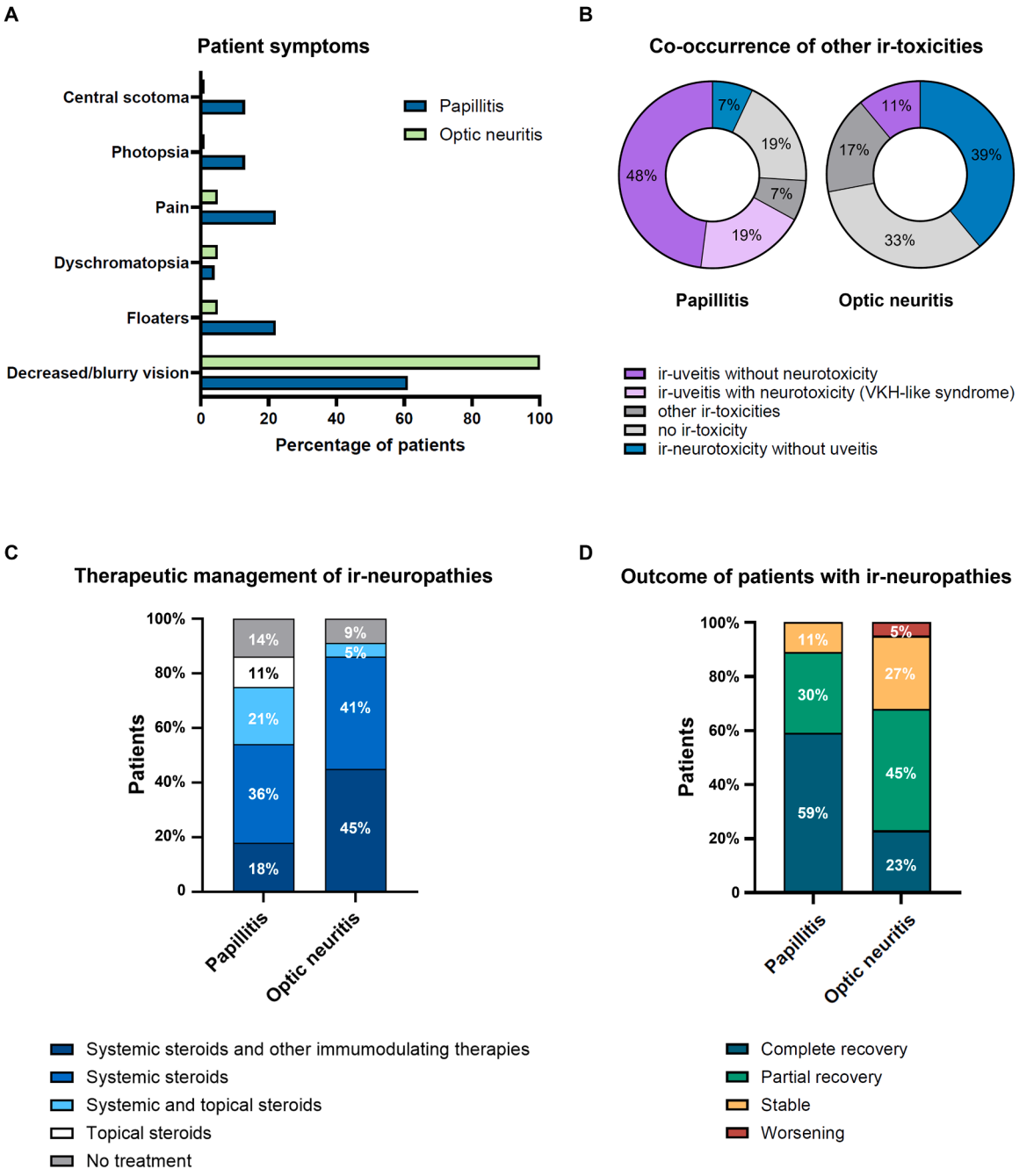

Fig. 4. Clinical characteristics and outcome of patients with ir-papillitis and ir-optic neuritis. (A) Clinical profile of the two groups of papillitis and optic neuritis shown as the number of patients experiencing the corresponding symptom. (B) Percentage of patients with the corresponding associated ir-toxicity in the two groups. Bar diagrams comparing management (C) and patient outcomes (D) in each subgroup. Percentages are calculated on the whole cohort of patients, from both systematic review and our case series (overall 50 patients).

In our series, we continued ICI with the same regimen in one patient due to rapid and complete recovery and reintroduced it in another patient after two months without recurrence. Overall (systematic review and our center series), seven patients with papillitis and two cases with optic neuropathy (14 %) were successfully rechallenged without optic neuropathy recurrence. However, three of the seven papillitis cases experienced uveitis recurrence upon ICI reintroduction, and one patient developed recurrent papillitis after steroid discontinuation.

These findings suggest that ICI therapy may be cautiously reintroduced after complete recovery from non-severe papillitis, provided there is no evidence of optic nerve involvement. In contrast, optic neuritis warrants greater caution due to the high risk of persistent visual deficits.

5. Conclusion

A bilateral optic nerve involvement with painless decline of vision and papilledema is the most common presentation of immune-related optic neuropathies. Two main clinical patterns can be distinguished: (i) papillitis, which is usually associated with other intraocular inflammation, and (ii) optic neuritis, which is more often associated with neurological immune-related toxicities and lead to a worse outcome. Given the good tolerability in reported cases, it seems safe to reintroduce ICIs after non-severe papillitis without evidence of optic nerve involvement. However, a careful risk-benefit analysis should be considered on a case-by-case basis.

Author's contributions

SC conceptualized the study, collected and analyzed data, and wrote the preliminary version of the paper. AV, EL, EP, GP and AC contributed to the collection of data. All authors participated in critical review and revision of the final manuscript.

CRediT authorship contribution statement

Giuseppe Aprile: Writing – review & editing, Data curation. **Céleste Lebbé:** Writing – review & editing. **Antoine F. Carpentier:** Writing – review & editing, Project administration. **Aude Couturier:** Writing – review & editing, Data curation. **Stefania Cuzzubbo:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Evelaine Louis:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Alberto Vogrig:** Writing – review & editing, Writing – original draft, Data curation. **Elise Philippakis:** Writing – review & editing, Data curation. **Emilien Ezine:** Writing – review & editing. **Renata Ursu:** Writing – review & editing.

Consent for publication

This manuscript does not contain any individual person's data. However, written informed consent was obtained from all patients.

Ethics approval and consent to participate

Melanoma patients of the series are registered in MelBase, a French clinical database with biobank of adult melanoma patients that was approved by the French ethics committee (CPP Ile-de-France XI, n°12027, 2012) and registered in the NIH clinical trials database (NCT02828202). The study was also approved by the Regional ethics committee of the Friuli Venezia Giulia Region, Italy (Ref. No. CEUR-2023-Os-102 "Neuro-Checkmate"). This study was performed in accordance with the Declaration of Helsinki.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests. CL and AFC are consultors for BMS; CL received honoraria from Gilead and Janssen. All remaining authors have declared no conflicts of interest'.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2026.116594.

Data availability

All data relevant to the study are included in the article. Any other data is available on request.

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