Immune checkpoint monoclonal antibody-related adverse effects in neuro-ophthalmology

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Abstract:

Immunotherapy has renovated the field of oncology. Usually, cancer is treated by surgery, chemotherapy, and radiation. Immunotherapy is a promising treatment that harnesses the patient's own immune system to target cancer. Immune checkpoint inhibitors (ICIs) have proven to be a promising treatment avenue for managing cancer; however, their use had been associated with a unique spectrum of adverse side effects called immune-related adverse events (irAEs). As ICIs become increasingly relevant in cancer management, it is crucial to address these irAEs affecting various systems in the body, including the skin, liver, gastrointestinal tract, endocrine system, and the eye. Ocular toxicity and sight-threatening events are among the reported irAEs, impacting diverse ocular tissues. The most commonly reported ocular irAEs (OirAEs) are blurred vision, conjunctivitis, ocular surface disease uveitis, scleritis, and retinopathy. Nevertheless, the frequency and severity of these OirAEs can vary, even within the same class of ICIs. Thus, OirAEs can significantly impact the quality of life and patient compliance. Therefore, we aim to comprehensively analyze uncommon and severe ICI-related OirAEs associated with lung cancer by providing a comprehensive and updated review of immune checkpoint monoclonal antibody-related adverse effects in neuro-ophthalmology irAEs. Through a review of the relevant literature, we intend to illustrate the epidemiology, clinical characteristics, contributory factors, diagnosis, and management of ICI-associated ocular side effects. We will also discuss guidelines and best practice strategies for the prevention, monitoring, and management of these OirAEs.

Keywords:

Immune checkpoint inhibitors ocular toxicities, immune-related adverse events, ocular toxicities

Introduction

The immune system plays a crucial role in monitoring and eliminating cancer cells. The first class of ICIs (ipilimumab) was Food and Drug Administration approved in 2011. However, tumor cells can outmaneuver this defense mechanism by upregulating immune checkpoints, which promotes immune tolerance. To counter this, immune checkpoint inhibitors (ICIs) are used to block inhibitory pathways such as cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1) programmed death-ligand 1 (PD-L1), and lymphocyte activating gene-3 (LAG3), reactivating the immune response to destroy tumors.

ICIs can also lead to overactivation of the immune system, resulting in immune-related adverse events (irAEs). These irAEs can affect various organs, including the skin, heart, lungs, liver, kidneys, central nervous, gastrointestinal, endocrine, musculoskeletal, hematological, and ocular systems. Common systemic irAEs include fatigue, skin pruritus, skin rash, lymphocytopenia, and abnormal liver function. These adverse events can vary in severity and manifest in diverse forms. The most common reported ocular irAEs (OirAEs) are blurred vision, conjunctivitis, ocular surface disease (such as dry eye, keratitis, and corneal perforation), uveitis, scleritis, retinal vascular occlusion, cystoid macular edema, retinal pigmented epithelium, and serous retinal detachment; whereas the most common neuro-ophthalmology irAEs (NOirAEs) are orbital inflammatory syndrome, thyroid orbitopathy, ocular myasthenia, and optic neuropathy.[1-3]

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Table 1: Common terminology criteria for adverse events

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mild	Moderate	Severe	Sight-threatening Life-threatening	Death
Asymptomatic or mild symptoms BCVA 20/20 Intervention not indicated	Symptomatic with moderate decrease in VA BCVA >20/40 or <3 lines of decreased vision from baseline Medical intervention indicated	Symptomatic with marked decrease in VA BCVA <20/40 or >3 lines of decreased vision from baseline (up to 20/200) Invasive intervention indicated	Life-threatening consequences BCVA <20/200 Urgent intervention indicated	Death

CTCAE v5.0 (version 5). VA: Visual acuity, BCVA: Best-corrected Visual acuity

Mechanism of Action

ICIs work by targeting specific proteins known as immune checkpoint proteins, which are a normal part of the immune system they play a critical role in modulating immune responses to prevent excessive tissue damage. The primary mechanism of immune checkpoint involves blocking the interactions between checkpoint proteins, which allows the immune system to mount a more robust attack against cancer cells or other threats.

T cells are activated when they recognize specific antigens present on the surface of cancer cells. To prevent overactivation of the immune system and potential damage to healthy tissues, there are checkpoint proteins on the surface of T cells and their target cells. The interaction between these checkpoint proteins regulates T cell activity. In some cases, cancer cells and other target cells express proteins such as PD-L1 or CTLA-4. When PD-L1 on the target cell binds to PD-1 on the T cell or when CTLA-4 on the T cell binds to CD80/CD86 on antigen-presenting cells, it sends an "off" signal to the T cell. This signal inhibits the T cell's ability to attack the target cell. The binding of checkpoint proteins essentially "turns off" T cell activity, allowing cancer cells to evade the immune system.

ICIs are designed to block the interactions between checkpoint proteins. For example, drugs such as pembrolizumab and nivolumab block the interaction between PD-1 on T cells and PD-L1 on target cells. Ipilimumab targets CTLA-4. By doing so, these inhibitors prevent the "off" signal from being sent, which allows the T cells to remain active and attack cancer cells more effectively. With the immune checkpoint inhibited, T cells are better equipped to recognize and attack cancer cells, resulting in an enhanced immune response against cancer. To date, there are 9 approved ICIs, targeting four different molecules, PDL-1, CTLA-4, PD-1, and LAG-3. LAG-3 is the newest marker and target of T cell induced B-cell activation; it inhibits CD4-dependent T cell function through its cytoplasmic domain.

These mechanisms enable the immune system to overcome the suppression imposed by cancer cells and mount a more potent attack, potentially leading to improved outcomes for cancer patients. However, it is worth noting that while ICIs have been successful in treating certain cancers, they may also lead to immune-related side effects due to the increased activity of the immune system. Monitoring and managing these side effects are an important aspect of using these therapies.[3-6]

Pathogenesis

The eye is one of the organs which possess immune privilege, a state of protection from immune responses that is facilitated by several factors including the presence of the blood–retinal barrier, the absence of efferent lymphatics, and the upregulation of molecules such as Fas ligand and tumor necrosis factor β in ocular tissues. These features collectively create a unique microenvironment within the eye that limits immune responses and protects ocular tissues.

However, despite its immune privilege, the eye is vulnerable to the effects of various immunotherapies. This susceptibility can be attributed to the delicately balanced homeostatic environment of growth factors and cell receptors within the eye. The eye's structures are highly specialized and differentiated with nearly 90% of the genes in the human genome being expressed in one or more of the eye's tissues. This intricacy makes the eye more susceptible to disruptions caused by immunotherapies.

In addition, the ability of vascular formation in the eye may contribute to its susceptibility. Angiogenesis is regulated tightly in ocular tissues to maintain their normal function. However, some immunotherapies can interfere with this process, leading to ocular complications such as retinal vascular occlusion, macular edema, and retinal detachment.

Understanding and carefully managing these potential adverse effects are essential to preserve visual function in patients receiving ICIs.[4]

Epidemiology of Ocular Immune-Related Adverse Events

Initially, the estimated incidence of OirAEs was approximately 1%. However, a recent study of 1000 patients at the Mayo Clinic reported a higher incidence of 2.8%, with dry eye, inflammatory uveitis, and myasthenia gravis (MG) being the most common OirAEs. Another study using the Federal Adverse Event Reporting System data from 2003 to 2018 found that atezolizumab had the highest association with overall eye inflammation, whereas ipilimumab had the highest association with uveitis specifically. In addition, the Intelligent Research in Sight (IRIS) registry from the American Academy of Ophthalmology (AAO), which included 112 patients with OirAEs, found that anterior uveitis had the highest incidence rates, especially in those with a prior history of ocular

inflammation. A study using the Kaiser Permanente database revealed a higher 1-year incidence of uveitis in melanoma patients (1.2%) than in the nonmelanoma cancer patients (0.2%) with an odds ratio of 6.45.

Regarding NOirAEs, a systemic review of 115 primary case reports and series by Yu *et al.* estimated the overall incidence to be approximately 0.46%. They divided the NOirAEs into afferent and efferent etiologies. The afferent NOirAEs included optic neuritis (12.8%), neuroretinitis (0.9%), and giant cell arteritis (GCA) (3.7%), whereas efferent NOirAEs comprised MG (45.0%), thyroid-like eye disease (12%), orbital myositis (13.8%), general myositis with ptosis (7%), internuclear ophthalmoplegia (0.9%), opsoclonus–myoclonus–ataxia syndrome (0.9%), and oculomotor nerve palsy (0.9%).[3,5,8]

Pembrolizumab, a PD-1 inhibitor, was identified as the most common causative agent for NOirAEs (32%). Most patients (80%) experienced improvement or complete resolution of neuro-ophthalmic symptoms on cessation of ICI and immunosuppression. The median time to symptom onset was two cycles of ICI therapy. ICIs were terminated in the majority of patients (62%), whereas treatment was held in 11% of patients and continued without pause in 12% of patients. At the last recorded follow-up, 41% of patients experienced an improvement in neuro-ophthalmic symptoms with persistent deficits (e.g., ptosis, diplopia, and optic nerve pallor) and 39% had complete resolution of neuro-ophthalmic symptoms. Overall, there are no consensus statements on the diagnosis and management of NOirAEs. Based on the Common Terminology Criteria for Adverse Events (CTCAE (found in Table 1, NOirAEs range from Grade 2 to Grade ranging from moderate to severe and sight threatening. Recommendations are based on Level V evidence (studies without a control group, case reports, and expert opinions) and Grade B level of recommendation (strong evidence for efficacy but with a limited clinical benefit). However, it is essential to rule out potential mimickers of these manifestations including primary cancer burden, metastasis, or non-ICI paraneoplastic etiology.[6,7]

Clinical Characteristics of Neuro-ophthalmology Immune-related Adverse Events

We will discuss the common, well-documented clinical characteristics of NOirAEs including optic neuropathy, GCA, thyroid eye disease (TED), and MG.

Optic neuropathy

ICI-associated optic neuropathy has typically been reported within the literature as either optic neuritis, nonarteritic anterior ischemic optic neuropathy, or arteritic anterior ischemic optic neuropathy GCA. ICI-associated optic neuritis appears to present differently. The typical presentation of optic neuritis includes an acute, unilateral, and painful (with eye movement) vision loss. However, according to a review by Francis *et al*.[16] of 11 patients, only 10% of patients reported painful vision loss, 67% color-vision defect, and 64% of patients had a bilateral presentation. Sixty percent of ICI-associated optic neuritis cases have been associated with ipilimumab and the median onset was after four cycles. All cases experienced resolution or improvement with residual symptoms or signs (e.g. visual defects and disc pallor) after discontinuation of ICI. ICI-associated optic neuritis neuroimaging including MRI brain and orbit with and without contrast with fat saturation, cerebrospinal fluid for cell count, protein, glucose, oligoclonal bands, viral polymerase chain reactions, flow cytometry and cytology, and paraneoplastic panel. Laboratory tests for Vitamin B12, copper, HIV, rapid plasma reagin (RPR), antinuclear antibodies (ANA), anti-Ro/La antibodies, aquaporin-4 immunoglobulin G (IgG), myelin oligodendrocyte glycoprotein IgG, and paraneoplastic panel. Treatment of ICI-associated optic neuritis includes inpatient care and permanently discontinuing immunotherapy. The mainstay for treatment is a high dose of corticosteroids followed by a slow prednisone taper.[7-9,12,15]

Giant cell arteritis

In ICI-associated GCA, patients present with typical manifestations including temporal tenderness, jaw claudication, and vision loss. However, these patients may also have no visual symptoms and can but usually do not present with symptoms of polymyalgia rheumatica. Examination findings may include optic neuropathy, diplopia, temporal tenderness, a weaker or absent temporal artery, or features of an ischemic stroke. ICI-associated GCA has been reported with nivolumab, ipilimumab, a combination of both, and pembrolizumab. The proposed pathophysiology of GCA lies in the high expression of PD-L1 in dendritic cells of normal arteries; arteries affected by GCA show low to no coinhibitory PD-L1 expression and they show high costimulatory CD80 (B7-1) and CD86 (B7-2) expression leading to unopposed T-cell activation. Furthermore, T cells within granulomas of GCA temporal arteries were PD-1 positive. These findings suggest that immune mediators may play a major role in GCA pathogenesis and can potentially identify targets for the treatment of GCA itself.

For ICI-associated GCA, workup includes erythrocyte sedimentation, C reactive protein, B-ultrasound of temporal arteries, and temporal artery biopsy. Treatment for ICI-associated GCA includes permanently discontinuing immunotherapy. The standard treatment for suspected GCA involves urgent high-dose IV corticosteroids and inpatient hospitalization as soon as the diagnosis is suspected followed by a slow prednisone taper due to significant morbidity. Further referral to rheumatology for consideration of tocilizumab, a monoclonal antibody against interleukin-6 receptor subunits can be used for refractory GCA.[9,10,15]

Thyroid eye disease

In IC-associated TED, the proposed mechanism of orbital fibroblast activation and resulting extraocular muscle enlargement is the same as for non-ICI TED. Further, the

clinical presentation is often identical to that of non-ICI TED including symptoms such as proptosis, diplopia, pain, resection of extraocular muscle movements, and conjunctival injection and will affect muscles in the same order (inferior rectus, medial rectus, superior, levator, lateral rectus, and oblique). ICI-associated TED is commonly associated with CTLA-4 use but has been reported with ipilimumab, pembrolizumab, and nivolumab. Given the similarity in presentation, treatment of ICI-associated TED also involves anti-inflammatory treatments (nonsteroidal anti-inflammatory agents, steroids, and other immunosuppressive medications) or teprotumumab, a monoclonal antibody against insulin growth-like factor.[11,14,15]

Myasthenia gravis

In ICI-associated MG, ophthalmic manifestations may be related to purely ocular MG or ocular features of generalized MG. Symptoms are variable and can include painless vision loss, diplopia, ptosis, or ophthalmoplegia. ICI-associated MG has been linked to PD-1 inhibitors. According to the review of NOirAEs by Francis *et al*., ICI-associated MG has the highest mortality rate (19.8%) due to its life-threatening systemic manifestations (respiratory distress, myasthenic crisis, etc.). Treatment of ICI-MG is similar to standard MG including acetylcholinesterase inhibitors and immunosuppressive therapies (mycophenolate, azathioprine, intravenous immunoglobulin, and plasmapheresis); however, longer-term, chronic immunosuppression might be required for ICI-MG.[13-16]

Conclusion

Understanding and effectively managing these ocular complications are essential for optimizing cancer therapy while ensuring the safety and well-being of patients in ICIs. Because of the relative rarity of these toxicities, overall long-term complications and prognosis are unknown. Some clinicians suggest routine ophthalmological examination every 6 months due to the possibility of ocular toxicities. Future research should focus on determining the minimal active dosages of ICIs required to achieve antitumor responses while limiting IRAEs. Rapid diagnosis and administration of immunosuppression can enhance patient outcomes. To manage these OirAEs, a coordinated effort and communication with oncology are crucial.

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Conflicts of interest

There are no conflicts of interest.

References

1. Zhou L, Wei X. Ocular immune-related adverse events associated with immune checkpoint inhibitors in lung cancer. Front Immunol 2021;12:701951.
2. Mazharuddin AA, Whyte AT, Gombos DS, Patel N, Razmandi A, Chaudhry AL, *et al.* Highlights on ocular toxicity of immune checkpoint inhibitors at a US tertiary cancer center. J Immunother Precis Oncol 2022;5:98-104.
3. Ameri M, Al Zubidi N, Razmandi A, Whyte A, Naing A, Patel NA, *et al.* Ocular toxicity profile of targeted cancer therapy (TCT) at a US tertiary cancer center. Cureus 2023;15:e40597.
4. Seidel JA, Otsuka A, Kabashima K. Anti-PD-1 and Anti-CTLA-4 therapies in cancer: Mechanisms of action, efficacy, and limitations. Front Oncol 2018;8:86.
5. Raheem F, Alsuhebany N, Hickey Zacholski E, Paulic N, Sandler A, Uk N, *et al.* Ocular toxicities associated with antibody drug conjugates and immunotherapy in oncology: clinical presentation, pathogenesis, and management strategies. Expert Opin Drug Saf 2023;22:921-8.
6. Winges KM and Gordon LK. Neuro-ophthalmic complications of immune checkpoint inhibitor therapy: Current status and future directions. Front. Ophthalmol. 2022;2:1044904. doi: 10.3389/fopht.2022.1044904.
7. Mancone S, Lycan T, Ahmed T, Topaloglu U, Dothard A, Petty WJ, *et al.* Severe neurologic complications of immune checkpoint inhibitors: A single-center review. J Neurol 2018;265:1636-42.
8. Yu CW, Yau M, Mezey N, Joarder I, Micieli JA. Neuro-ophthalmic complications of immune checkpoint inhibitors: A systematic review. Eye Brain 2020;12:139-67.
9. Reynolds KL, Guidon AC. Diagnosis and management of immune checkpoint inhibitor-associated neurologic toxicity: Illustrative case and review of the literature. Oncologist 2019;24:435-43.
10. Goldstein BL, Gedmintas L, Todd DJ. Drug-associated polymyalgia rheumatica/giant cell arteritis occurring in two patients after treatment with ipilimumab, an antagonist of ctla-4. Arthritis Rheumatol 2014;66:768-9.
11. Safa H, Johnson DH, Trinh VA, Rodgers TE, Lin H, Suarez-Almazor ME, *et al.* Immune checkpoint inhibitor related myasthenia gravis: Single center experience and systematic review of the literature. J Immunother Cancer 2019;7:319.
12. Common Terminology Criteria for Adverse Events (CTCAE). Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5×7.pdf. [Last accessed on 2023 Nov 21].
13. Vishnevskia-Dai V, Rozner L, Berger R, Jaron Z, Elyashiv S, Markel G, *et al*. Ocular side effects of novel anti-cancer biological therapies. Sci Rep 2021;11:1-7. Available from: https://www.nature.com/articles/s41598-020-80898-7. [Last accessed on 2023 Nov 21].
14. Mancone S, Lycan T, Ahmed T, Topaloglu U, Dothard A, Petty WJ, Strowd RE. Severe neurologic complications of immune checkpoint inhibitors: a single-center review. J Neurol 2018;265:1636-42. doi: 10.1007/s00415-018-8890-z.
15. Villamil-Jarauta M, Sierra-Mercado M, Santiago MA, MD, Ramirez-Vick M, Gonzalez-Rodriguez L. Thyroid disease after immune checkpoint inhibitor therapy. Endocrine Practice, 2018;24:230. Available from http://www5.sph.uth.tmc.edu:2048/login?url=https://www.proquest.com/scholarly-journals/thyroid-disease-after-immune-checkpoint-inhibitor/docview/2050599770/se-2. [Last accessed on 2023 Nov 23].
16. Francis JH, Jaben K, Santomasso BD, Canestraro J, Abramson DH, Chapman PB, Berkenstock M, Aronow ME. Immune Checkpoint Inhibitor-Associated Optic Neuritis. Ophthalmology. 2020;127:1585-89.