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Case Report

When Uveitis and Hypotony Meets Bilateral Iris Retraction Syndrome: A Rare but Serious Complication of Nivolumab Treatment

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Abstract
Introduction: Iris retraction syndrome (IRS) is a rare clinical condition characterized by a backbowing of the iris positioned on the lens with a complete pupillary block. Immune checkpoint inhibitors (ICIs) are a new class of immunomodulating agents used in cancer therapy, and although they have high response rates, ophthalmic-related side effects have been reported. We report a rare case of bilateral IRS with hypotony after therapy with nivolumab. ***Case Presentation:*** We present a case of bilateral IRS with hypotony, 3 mm Hg OD and 5 mm Hg OS, after therapy with nivolumab. The patient presented with decreased vision, corneal edema, keratic precipitates, deep anterior chamber with posterior synechiae, and hypotony maculopathy. Anterior segment OCT revealed a sharp posterior displacement of the iridolenticular diaphragm consistent with IRS. Discontinuation of nivolumab until ocular improvement was suggested, following oncologic consultation. Four months later, the patient exhibited iris bombé with angle closure and increased IOP. This was managed with phacoemulsification and concomitant surgical iridectomy. One month after surgery, the patient's IOP had returned to physiologic values, and the iris configuration had returned to normal. ***Conclusion:*** The exact mechanism of IRS remains unclear, but it is suggested that an aqueous imbalance, in conjunction with uveitis and hypotony, creates an anterio-posterior movement of the iridolenticular diaphragm when the pupillary block is present. Our case highlights the importance of

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monitoring patients receiving ICIs for ophthalmic adverse effects and prompt management to prevent permanent visual damage. In conclusion, this is the first reported case of IRS after therapy with ICIs. Further research is needed to fully understand the exact mechanism by which it is induced.

Introduction

Iris retraction syndrome (IRS) is a rare clinical condition characterized by a backbowing of the iris positioned on the lens with complete pupillary block [1]. This can be seen in post-surgical and non-surgical conditions, resulting in a significant deepening of the anterior chamber (AC) [2]. IRS mechanism remains unclear, but an aqueous imbalance creates an anterio-posterior movement of the iridolenticular diaphragm in conjunction with complete pupillary block [1–4]. A new class of immunomodulating agents called immune checkpoint inhibitors (ICIs) is transforming anti-cancer therapy. Within this class, two prominent examples are highlighted; ipilimumab (Yervoy; Bristol-Myers Squibb, New York, NY, USA), which targets anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), and nivolumab (Opdivo, Bristol-Myers Squibb), which is designed to target programmed cell death protein-1 (PD-1) [5]. We report a rare case of bilateral IRS with hypotony after therapy with nivolumab.

Case Report

A 58-year-old man presented to our clinic in December 2022 with decreased vision. His medical history included hypertension, diabetes mellitus, hypothyroidism and hip osteoarthritis, under treatment, as well as mesothelioma, for which he was given chemotherapy (November 2021) before switching to ICIs ipilimumab and nivolumab in January 2022. After the first round of ICIs, he presented facial nerve paresis as a side effect of ipilimumab, resulting in its discontinuation. His best corrected visual acuity (BCVA) was 1/10 OD and 3/10 OS. Slit-lamp examination revealed corneal edema with Descemet fishnet-like striae, keratic precipitates (KPs), pigment deposits on the lens and flare 2+ in both eyes. The AC was deep with 360° posterior synechiae and a nuclear sclerotic cataract (2+) (Fig. 1a). His intraocular pressure (IOP) was 3 mm Hg OD and 5 mm Hg OS, while B-scan showed a serous retinal detachment (SRD) in his right eye. Further workup demonstrated fine striae due to hypotony maculopathy on OCT and optic disk edema on OCT-RNFL analysis. Fluorescein angiography results revealed late leakage originating from the optic disc with poorly defined borders, indicative of optic disc swelling, in both eyes (OU). Notably, no indications of vasculitis were identified. Indocyanine green angiography findings indicate the absence of any evidence of inflammation in the choroidal or choriocapillaris regions (Fig. 2). Anterior segment OCT was additionally performed, depicting a sharp posterior displacement of the iridolenticular diaphragm, consistent with iris retraction syndrome (IRS) (Fig. 1b). Finally, gonioscopy examination revealed a 360° wide open angle with blood in Schlemm's canal in both eyes. Therapeutically, topical dexamethasone, cyclopentolate and artificial tears were initiated. The following day corneal edema was improved with no sign of fishnet-like striae, KPs, or flare in the AC, while his BCVA and IOP remained the same. Methylprednisolone per OS was added to his therapy and was slowly tapered down. On consultation with the patient's oncologists, discontinuation of nivolumab until ocular improvement was suggested. The patient did not

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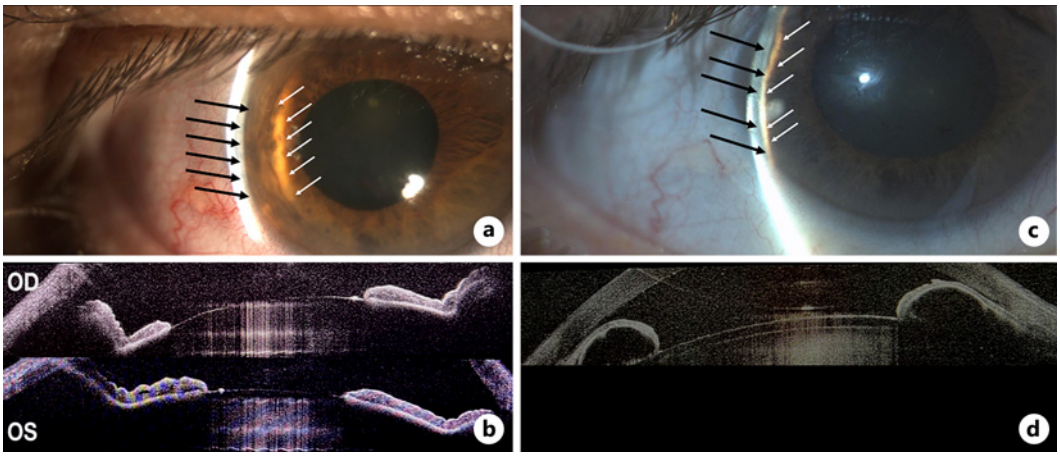

Fig. 1. a Slit-lamp photograph of the right eye showing irregular iris morphology with posterior bowing and posterior synechiae at the pupillary margin. The AC depth is notably deep (between black and white arrows), suggesting hypotony. **b** Anterior segment OCT image of both eyes, demonstrating a sharp posterior displacement of the iridolenticular diaphragm, consistent with iris retraction syndrome. **c** Slit-lamp image of the right eye, exhibiting an iris bombé morphology and a very shallow AC depth (between black and white arrows). **d** Anterior segment OCT image of the right eye, highlighting the transition of iris morphology to an iris bombé configuration with a closed angle.

attend the 1-month follow-up appointment. Three months later, the patient's right eye exhibited an increased IOP of 45 mm Hg, while the left eye maintained a stable IOP of 16 mm Hg. He also reported IOP fluctuations during the period of missed appointments, which were temporarily managed with aqueous suppressant therapy, primarily acetazolamide tablets. The right eye showed an iris bombé configuration and closed angle (Fig. 1c, d), whereas the left eye did not exhibit similar configuration and had an open angle. The patient's BCVA was 1/10 in the right eye and 6/10 in the left eye. Given the patient's progression from IRS to iris bombe and back to IRS after treatment with aqueous suppressants due to hypotony, pupillary block, and nivolumab toxicity, the primary recommendation was to discontinue nivolumab therapy, followed by phacoemulsification and surgical iridectomy in the right eye. One month after surgery, the patient's IOP was 14 mm Hg in the right eye and 15 mm Hg in the left eye, and no inflammation was observed in the AC. Iris configuration had returned to normal, and the angle had opened.

Discussion

Iris retraction syndrome was first described in 1984, as a deepening of the AC and a retracted iridolenticular diaphragm with total pupillary block [1]. Pupillary block plays a crucial role for IRS, as it isolates the AC from the posterior chamber (PC). Depending on the hydrodynamics, iris morphology can change from iris bombé to IRS when aqueous production is suppressed. Notably, taking into account our patient's history of IOP fluctuations that were temporarily treated with aqueous suppressants, a change in iris morphology was observed, shifting between iris bombé and high IOP to hypotony and IRS at different time points (Fig. 1). This posterior bowing of the iris together with generalized contact with the lens has been confirmed via UBM scans [3]. Inflammation has been proposed as a crucial mechanism inducing ciliary shutdown and consequently hypotony, which leads to retrograde flow from the episcleral venous plexus. This shift in intraocular hydrodynamics may contribute to the

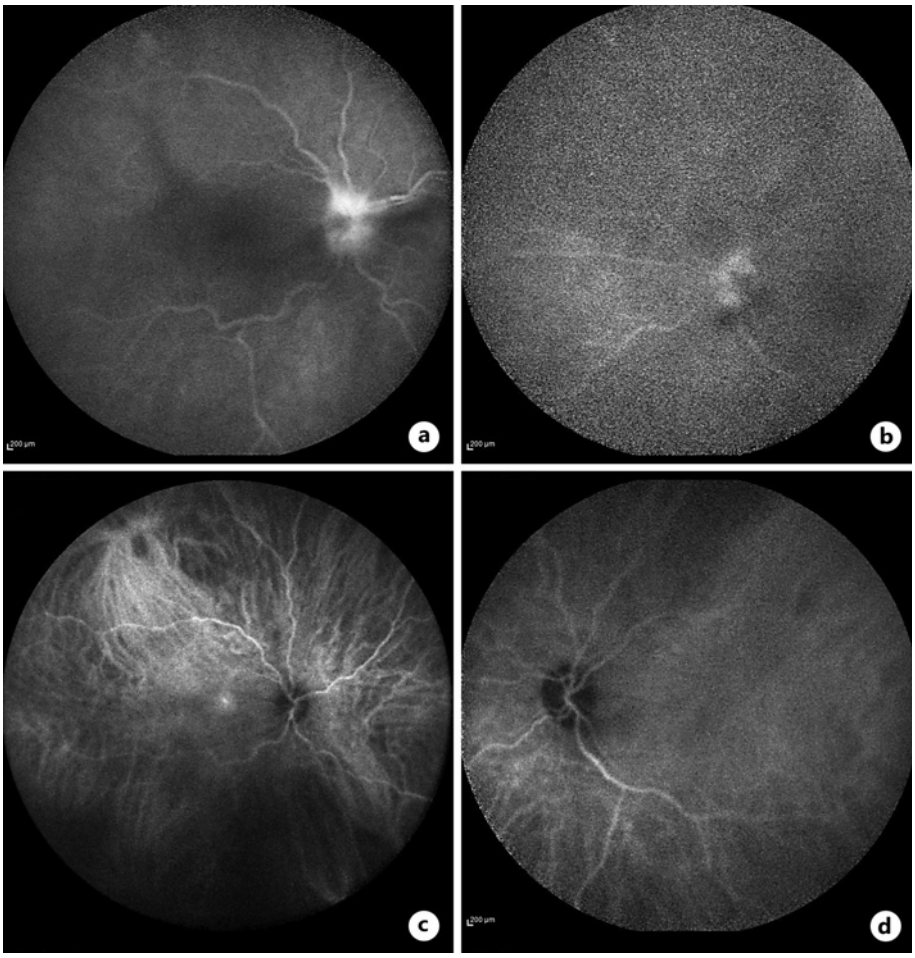

Fig. 2. a Fluorescein angiography image of the right eye, illustrating late leakage emanating from the optic disc with indistinct borders delineating optic nerve borders, indicative of optic disc swelling, and notably devoid of vasculitis indicators. **b** Corresponding image of the left eye. **c**, **d** Indocyanine green angiography images of both eyes, revealing an absence of choroidal or choriocapillaris inflammation.

deepening of the AC. Moreover, the formation of 360° posterior synechiae, resulting in isolation of the AC from the PC, may play a role in producing the characteristic morphology of IRS. By connecting these mechanisms, we can better understand the complex interplay, leading to the manifestation of IRS. Characteristically, breaking the pupillary block restores normal iridolenticular morphology and AC depth before the resolution of SRD [4]. In accordance, a case was reported, where normal iridolenticular morphology and AC depth were re-established after the reversal of pupillary block and before the restoration of rhegmatogenous retinal detachment [6]. Cases of IRS occurring in eyes that had undergone intraocular surgery are also documented [2, 7].

ICIs are a relatively new anti-cancer therapy with good response rates, but with several immune related adverse effects [5, 8, 9]. Although rare, ophthalmic adverse effects may be serious and potentially vision threatening [5, 10]. Nivolumab inhibits receptor PD-1, which is expressed on T-cells membrane and play an integral part in immunosuppression [11]. A study showed that PD-L1 receptors are widely expressed on several ocular tissues including the cornea, iris, ciliary body and RPE [12]. The mechanisms employed by the eye to prevent infection and inflammation render it an immune-privileged tissue. As a result, blocking the

PD-1/PD-L1 interaction could potentially lead to an immune adverse reaction against ocular tissues [5]. Only 2 case reports have described bilateral hypotony, cataract, and uveitis after ICI therapy; one after pembrolizumab (anti-PD-1) and the other after ipilimumab and nivolumab [13, 14]. Of note, neither of the aforementioned patients developed the characteristic morphology of IRS, in spite of presenting similar clinical findings with our patient. While considering Vogt-Koyanagi-Harada (VKH)-like adverse reactions to ICIs as a potential differential diagnosis, it is noteworthy that most ICIs associated with VKH-like adverse reactions have been primarily observed in the context of melanoma therapy [5, 8, 9]. Our patient's case differs in some key aspects. Notably, VKH is typically linked to an autoimmune reaction against melanocytes, which often manifest as vitiligo. Contrary to this our patient did not have vitiligo and was treated for mesothelioma. Additionally, while VKH and VKH-like can cause narrow AC, a deep posterior displacement of the iridolenticular diaphragm is atypical. Furthermore, fluorescein angiography and indocyanine green angiography findings were not supported for VKH and VKH-like syndromes (Fig. 2). In conclusion, given the unique characteristics and clinical course of our case, while we cannot entirely exclude the possibility of VKH and VKH-like syndrome, we consider it highly unlikely in this context. The exact mechanism behind IRS remains unclear. The presence of a SRD on the right eye with no sign of detachment on the left eye in our case, renders the necessity of retinal detachment in the pathogenesis of IRS questionable. Indeed, the combination of inflammation with total pupillary block and hypotony, appears to be the key modifiable factor in the development of IRS. Specifically, inflammation leads to ciliary shutdown and ultimately to a decrease in aqueous production. The resulting hypotony enables a retrograde flow from the episcleral vessels through the trabeculum [15], which in turn causes a shift in the intraocular hydrodynamics from the isolated anterior to the posterior chamber. This shift causes the iridolenticular diaphragm to be pushed backwards, deepening the AC and producing this characteristic morphology (Fig. 1a, b). In addition, as previously reported [1], the use of aqueous suppressants can significantly impact the intraocular hydrodynamics and consequently, the morphology of the iris. During our initial examination, active inflammation caused pupillary block and ciliary shutdown leading to hypotony and IRS morphology. However, at the 4-month follow-up, the absence of active inflammation led to a change in intraocular hydrodynamics, resulting in high IOP with iris bombé morphology (Fig. 1b, d). Conversely, when aqueous suppressants were present, hypotony with IRS morphology was again observed. The use of anterior segment OCT technology has confirmed, for the first time, the changes in iris morphology previously depicted in Campbell's 1984 drawings. To recapitulate, iris retraction syndrome consists the final clinical presentation of a consequence of events including: inflammation, uveitis, ciliary body shutdown, and hypotony.

The first step in the management of ICI ophthalmic adverse effects is to consider drug discontinuation, depending on their severity and after consulting an oncologist. The standard approach in such cases consists of topical and oral corticosteroid therapy, with most patients responding well [5, 8, 9]. Regarding the breakage of the pupillary block and the consequent resolution of IRS morphology, pupillary dilation has been suggested [4]. However, in our case, pupillary dilation did not prove effective. Given the occurrence of IRS even in pseudophakic eyes [2] and considering our patient's presentation with declining vision due to cataract, a comprehensive therapeutic strategy was adopted. This included phacoemulsification to enhance visual acuity, the dissolution of posterior synechiae, and concurrent surgical iridectomy to mitigate the formation of posterior synechiae. This multidimensional approach was deemed the definitive treatment, resulting in notable improvement in the patient's condition. Subsequent to 1 month of follow-up, IOP stabilized at 14 mm Hg, accompanied by the observation of consistently normal iris morphology devoid of inflammation. This outcome underscores the efficacy of the combined surgical interventions compared to performing solely a peripheral iridectomy as it ensures sustained improvements in both IOP and iris morphology.

In conclusion, this is the first reported case of iris retraction syndrome after therapy with immune checkpoint inhibitors, such as nivolumab. Further research is needed to fully understand the exact mechanism by which it is induced, while the rarity of such cases being documented may still warrant attention from the ophthalmology community.

CARE Checklist

The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000539425).

Statement of Ethics

This study protocol was reviewed and approved by the Ethics Committee of the General Hospital of Athens "Georgios Gennimatas" and was conducted in accordance with the Declaration of Helsinki, Approval No. 28399 – December 12, 2022. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images. This report does not contain any personal information that could lead to the identification of the patient.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conceptualization: S.A.K. and P.P.; methodology: S.A.K. and L.D.; validation: L.D. and S.D.; formal analysis: G.K. and P.P.; investigation: L.D. and P.M.; data curation: G.K. and S.D.; writing – original draft preparation: S.A.K., L.D., and P.P.; writing – review and editing: S.D. and P.M.; visualization and supervision: I.G. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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