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Unilateral acute iris transillumination syndrome with glaucoma and iris pigment epithelium dispersion simulating iris melanoma

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ABSTRACT

Purpose: To report a patient with a unilateral presentation of glaucoma, pain, and acute iris transillumination syndrome simulating iris melanoma.

Observations: A 53-year-old male presented with blurred vision and pain in his right eye several weeks following a respiratory sinus infection managed by oral azithromycin. Examination of the right eye was notable for elevated intraocular pressure of 46 mm Hg, an irregular mid-dilated pupil, and diffuse iris transillumination with pigmentary seeding on the iris surface, in the anterior chamber angle, and on the sclera, suspicious for diffuse iris melanoma with glaucoma and extrascleral extension. Ultrasound biomicroscopy (UBM) of the right eye revealed circumferential anterior chamber angle and trabecular meshwork involvement by an infiltrative process corresponding to the pigmented cells noted clinically, while the ciliary body was unremarkable. Following enucleation, histopathology showed extensive necrosis of the iris pigment epithelium, sphincter, and dilator muscles with melanophagic infiltration in the anterior chamber angle and episclera, mild chronic non-granulomatous iridocyclitis, and no evidence of a melanocytic neoplasm. Although immunohistochemical studies for herpes simplex virus (HSV) types 1 and 2, varicella-zoster virus, and cytomegalovirus were negative, qualitative real-time polymerase chain reaction on paraffin-embedded tissue detected HSV-1 DNA. The combined clinical, pathologic, and molecular findings were compatible with unilateral acute iris transillumination syndrome, likely HSV-1 associated.

Conclusion and Importance: Unilateral acute iris transillumination syndrome with diffuse iris pigment epithelial loss can simulate iris melanoma. Prompt herpes viral studies may be informative.

1. Introduction

Bilateral acute iris transillumination (BAIT) and bilateral acute depigmentation of the iris (BADI) are recently recognized clinical syndromes characterized by bilateral acute onset of ocular pain, severe photophobia, red eye, and pigment dispersion from the iris pigment epithelium (IPE) (BAIT) and iris stroma (BADI), with pigment deposition in anterior chamber structures.[1,2] While the etiology of BAIT and BADI remains unclear, these entities have been linked to upper respiratory tract infections, systemic and local antibiotic therapy and environmental toxins.[3–6] Viral etiology, including herpes viral infection, has been suggested to play a role in BAIT and BADI, but conclusive evidence is lacking.[1,7,8] BAIT and BADI can present with asymmetric ocular involvement and rarely unilaterally.[8,9] Herein, we report a patient with unilateral acute iris transillumination defects, likely related to herpes simplex virus type 1 (HSV-1) infection, which simulated iris melanoma.

2. Case report

A 53-year-old male with no prior ocular history developed redness,

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pain, and blurred vision in the right eye one to two weeks after a course of oral azithromycin for a respiratory sinus infection. At the time of initial evaluation, the patient was documented to have an intraocular pressure of 46 mm Hg and iritis (not further specified), prompting initiation of difluprednate, brimonidine, and timolol drops. Three months later a pigmented iris lesion in the right eye was noted by another provider and the patient was referred to the Ocular Oncology Service at Wills Eye Hospital.

On presentation, visual acuity in the affected right eye was 20/60 and 20/40 in the left eye. The intraocular pressure was 24 mm Hg in the right eye and 18 mm Hg in the left eye. The left eye showed nuclear sclerotic cataract and was otherwise unremarkable. The findings were limited to the right eye. The right pupil was mid-dilated, irregular, and poorly reactive (Fig. 1) with no relative afferent pupillary defect. There were episcleral pigment deposits around vessels on the globe surface, extensive pigment dusting on the iris stromal surface, and diffuse IPE transillumination defects on retroillumination (Fig. 1). There was no corneal infiltration, Krukenberg spindle, keratic precipitates, anterior chamber cells, or iris stromal atrophy. Gonioscopy showed circumferential dense pigmentation in the trabecular meshwork (Fig. 2). Dilated ophthalmoscopy of the right eye was unremarkable (Figs. 1 and 2).

Imaging with anterior segment optical coherence tomography (AS-OCT) and ultrasound biomicroscopy (UBM) of the right eye revealed circumferential anterior chamber angle and trabecular meshwork involvement by an infiltrative process corresponding to the pigmented cells noted clinically, while the ciliary body was unremarkable (Fig. 3). The anterior chamber angle was anatomically open and there was no posterior bowing of the iris that often accompanies pigment dispersion syndrome (Fig. 3). A suspected diagnosis of iris root/trabecular meshwork malignant melanoma with extraocular extension was made. The iris transillumination defects were presumed to be secondary to IPE necrosis from ischemia-induced high intraocular pressure. Various management options were discussed with the patient, including fine needle aspiration biopsy for cytological confirmation or enucleation, plaque brachytherapy, and observation. In light of the suspected diagnosis of iris root melanoma with diffuse trabecular meshwork seeding, extraocular extension, and elevated intraocular pressure off glaucoma medications, the patient elected to undergo enucleation.

Gross and microscopic evaluation of the globe revealed marked necrosis and segmental loss of the IPE (Figs. 3 and 4). Intensely pigmented cells (melanophages) were present within the trabecular meshwork. canal of Schlemm, anterior chamber angle, iris stromal surface, zonular fibers and episcleral surface (Figs. 3 and 4). Iris dilator and sphincter muscles were diffusely necrotic. Rare deep stromal vessels in the iris pupillary region were necrotic and the adjacent iris stroma was mildly hypocellular (Fig. 4). A sparse lymphocytic infiltrate was noted in the stroma of the iris root and in the adjacent pars plicata of the ciliary body (Fig. 4). The anterior chamber angle was anatomically open but contained a dense melanophagic infiltration. Other ocular tissues including the pars plana, choroid, retina, and optic nerve were unremarkable. There was no evidence of melanocytic neoplasm, keratic precipitates, granulomatous inflammation, or herpes-viral cytopathic effect.

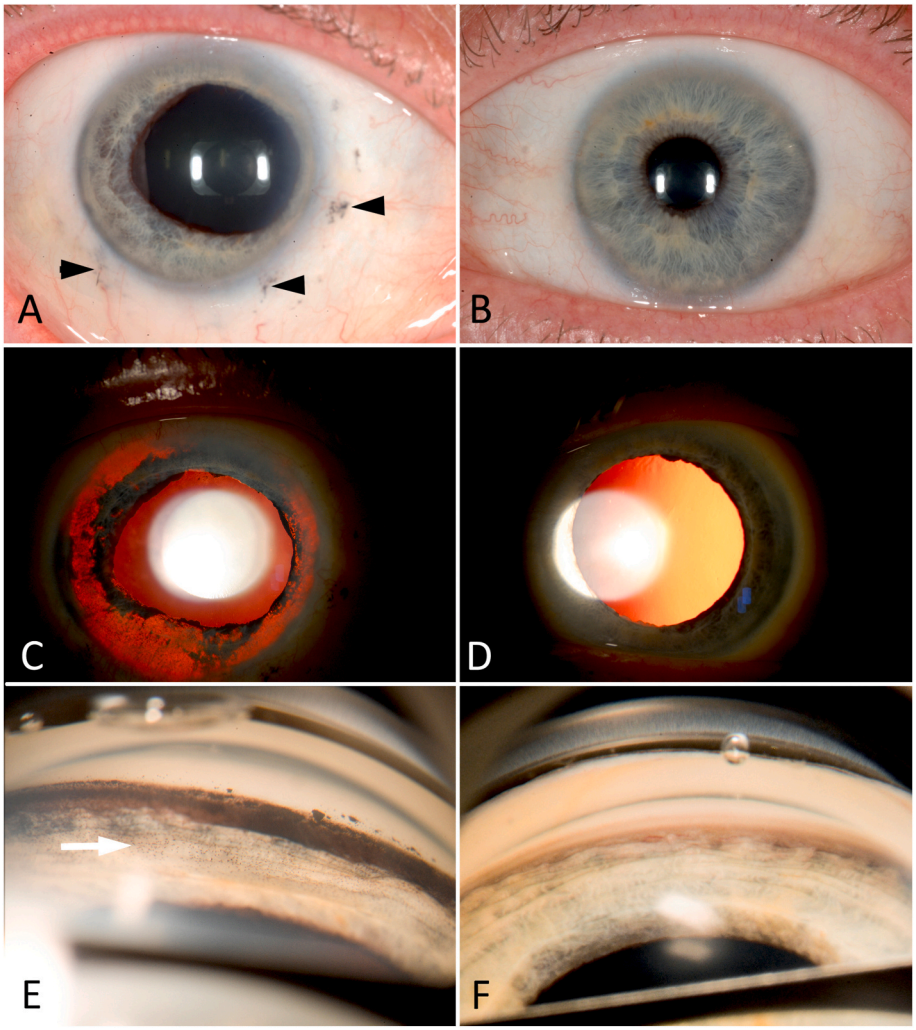

Fig. 1. Unilateral acute iris transillumination, clinical findings. A, The right eye showing a mydriatic, irregular pupil and multiple foci of episcleral pigment (arrowheads) adjacent to mildly dilated vessels. There is no appreciable iris stromal atrophy. **B,** Normal anterior segment of the left eye. **C,** Retroillumination of the right eye showing diffuse iris transillumination. D, Retroillumination of the left eye was normal. **E,** Gonioscopy of the right eye showing intense diffuse pigmentation of the angle with pigment dusting along the iris stroma (arrow). **F,** Gonioscopy of the left eye angle is without pigment deposition.

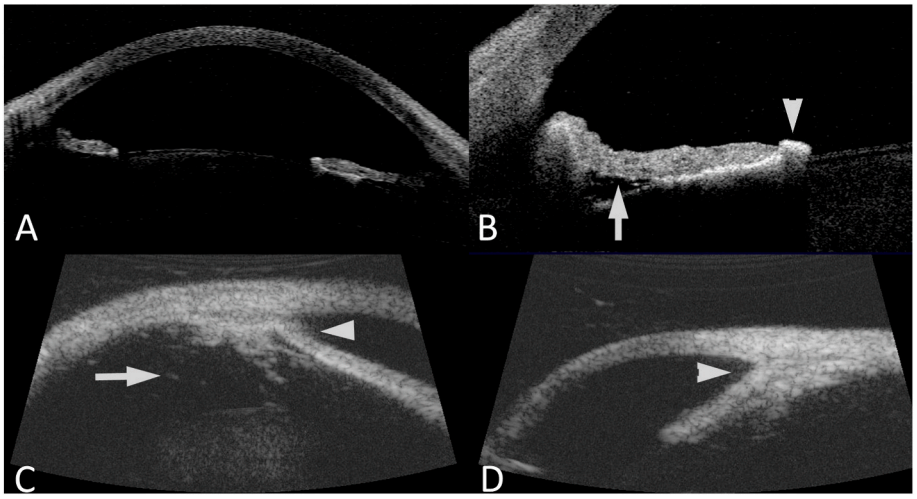

Fig. 2. Unilateral acute iris transillumination, imaging findings. **A,** Enhanced depth imaging anterior segment optical coherence tomography (AS-OCT) of the right eye showing a lack of posterior bowing of the iris surface. **B,** Higher magnification shows clumping of the iris pigment epithelium along the pupillary margin (arrowhead), focal disruption and absence of the iris pigment epithelium (arrow) and thickening of the adjacent iris root. **C,** Anterior segment ultrasound biomicroscopy (UBM) showing thickening of the inferior anterior chamber angle structures (arrowhead) and hyper-reflective foci (arrow) suggestive of pigmented cell dispersion adjacent to the unremarkable ciliary body. **D,** UBM of the inferior anterior chamber angle shows thickening of the iris root and effacement of the anterior chamber angle structures (arrowhead).

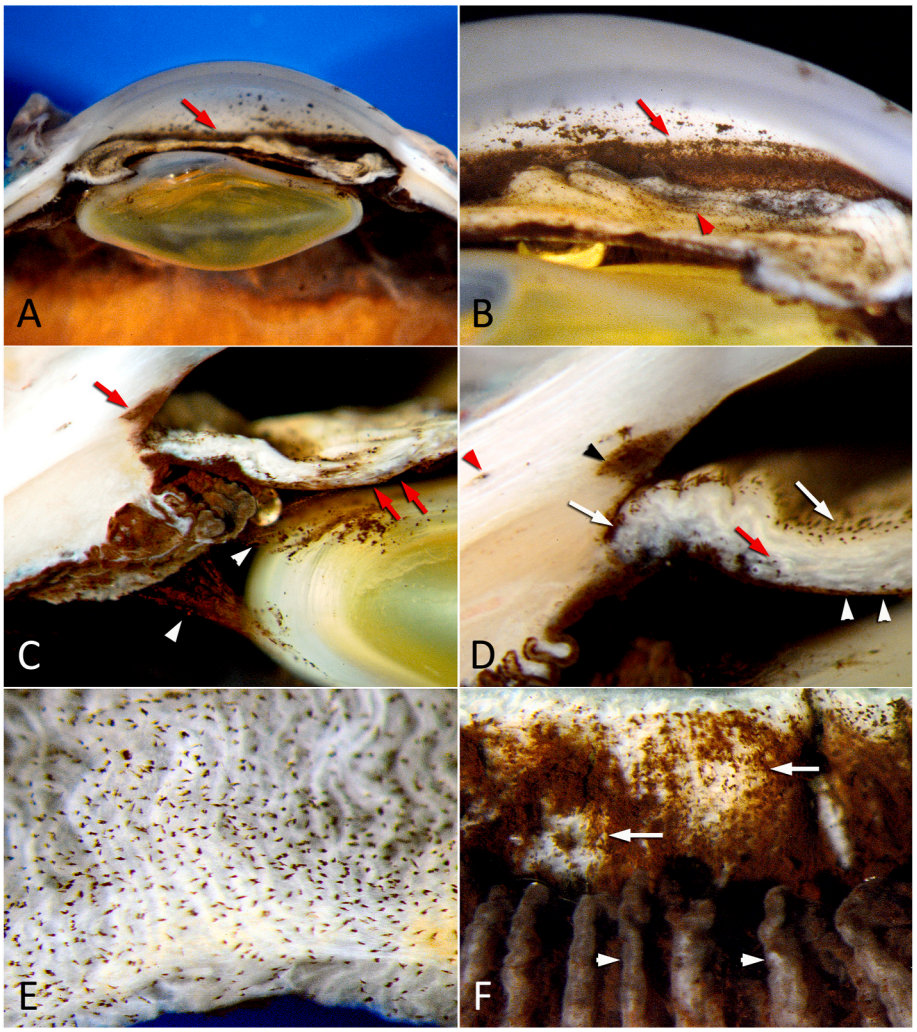

Fig. 3. Unilateral acute iris transillumination, macroscopic findings. **A,** Diffuse intense pigment in the anterior chamber angle (red arrow). **B,** Higher magnification highlights anterior chamber angle pigment (red arrow) and dusting of pigment on the surface of the iris (red arrowhead). **C,** Sectioned trabecular meshwork is filled with pigment (single red arrow). Pigment is seen on lens zonular fibers (white arrhoweads). Iris pigment epithelium is markedly disrupted and focally absent (two red arrows). **D,** Higher magnification shows focal absence of iris pigment epithelium (white arrowheads) and pigment deposits in the iris stroma (red arrow), on the anterior surface of the iris (white arrows), within the trabecular meshwork (black arrowhead), and intrascleral emissarial canals (red arrowhead). **E,** Scattered pigmented cells on the surface of the iris. **F,** The underside of the iris shows patchy areas of depigmentation with loss of iris pigment epithelium (arrows). The underlying ciliary processes of pars plicata (arrowheads) are unremarkable. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Immunohistochemical studies for HSV-1/2, varicella-zoster virus (VZV), and cytomegalovirus were negative. Molecular testing for *Toxoplasma* spp., cytomegalovirus, VZV, HSV-1, and HSV-2 was performed on formalin fixed paraffin embedded tissue by multiplex real time polymerase chain reaction (PCR) (Lightcylcer 2.0, Roche). DNA from HSV-1 was detected. Based on combined clinical history, clinical examination, histopathologic, and molecular findings, we interpreted this case as unilateral acute iris transillumination syndrome (UAIT), likely HSV-1 related. Eleven years later, the patient is doing well with 20/25 vision in his healthy left eye.

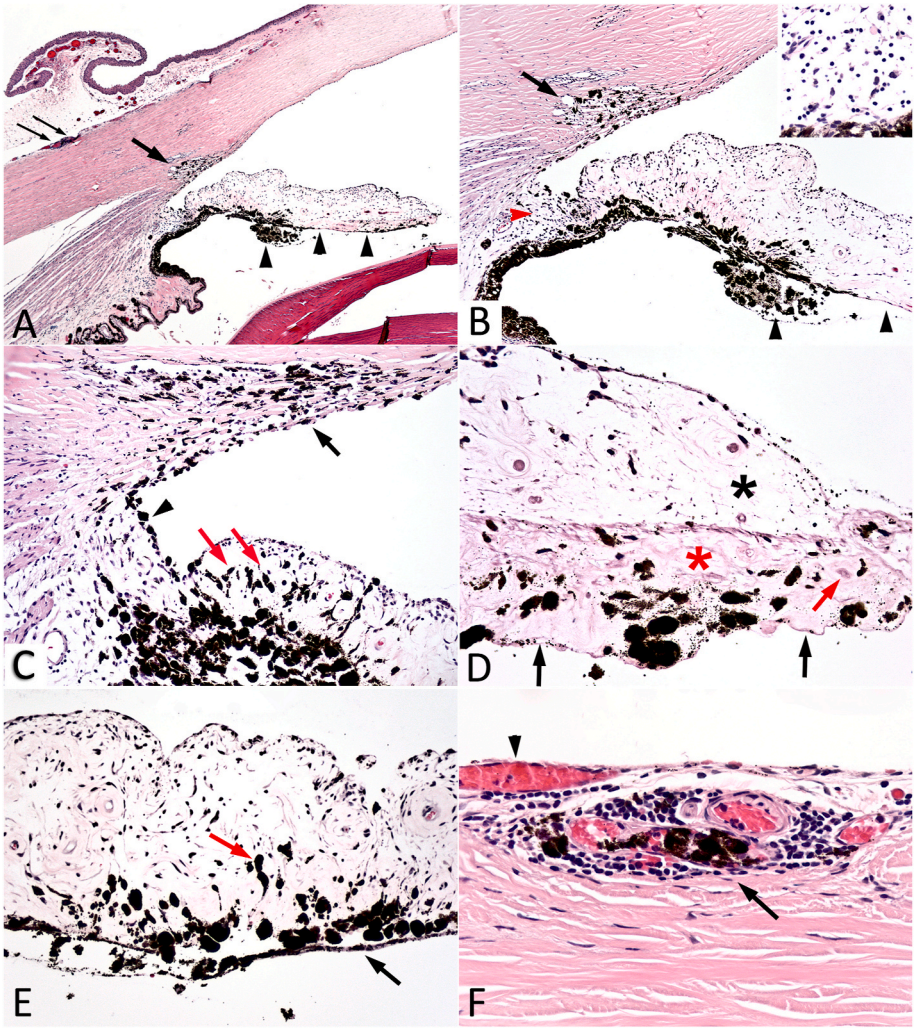

Fig. 4. Unilateral acute iris transillumination, histopathologic findings. **A,** Markedly disrupted and focally absent iris pigment epithelium (arrowheads), pigment in the anterior chamber angle (single thick arrow), and on epibulbar surface (two thin arrows). **B,** Higher magnification highlights absent and clumped iris pigment epithelium (black arrowheads), and melanophages within the trabecular meshwork (arrow). There is a sparse lymphocytic infiltrate in the iris root (red arrowhead), magnified in an inset. **C,** Higher magnification of the anterior chamber angle shows melanophagic infiltrate in the trabecular meshwork (black arrow), on the surface of the iris root (arrowhead), and in the iris stroma (two red arrows). Disrupted iris pigment epithelium at the bottom of the image. **D,** Pupillary portion of the iris showing extensive necrosis of the iris sphincter (red asterisk), associated with an infiltrate of intensely pigmented melanophages, focal vascular occlusion (red arrow), and stromal paucicellularity (black asterisk). Iris pigment epithelium is essentially absent (black arrows). **E,** Body of the iris showing disruption and loss of iris pigment epithelium (black arrow) with a melanophagic infiltrate in the overlying stroma (red arrow). There is absence (necrosis) of the dilator muscle. **F,** Cluster of darkly pigmented melanophages (arrow) and small dark blue lymphocytes surround episcleral vessels, which are focally dilated (arrowhead). [hematoxylin-eosin; 100x (A), 200x (B), 400x (C, E, F), 630x (D, B-inset)]. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

3. Discussion

We describe an unusual presentation of unilateral acute iris transillumination (UAIT) with extensive pigment dispersion even to the episcleral region that simulated diffuse iris melanoma, leading to enucleation. In addition to melanoma of the iris root with trabecular meshwork seeding and extraocular extension, the clinical differential diagnosis in our patient included a unilateral variant of BAIT syndrome and herpes virus-associated iritis. However, the clinical picture was not typical of either of these entities, leading to a diagnostic conundrum.

The diagnosis of BAIT and BADI is based on clinical features as there are no histopathologic studies to date. These syndromes might represent a spectrum featuring unilateral or bilateral iris transillumination (BAIT) and iris depigmentation without transillumination (BADI).[1] Although by definition bilateral, as most affected patients have had bilateral disease, asymmetric and unilateral presentation has been reported.[3,8–12] The etiology remains unknown. Several studies have shown an association with prior therapy with oral antibiotics days to weeks preceding the syndrome, most commonly moxifloxacin and less frequently other antibiotics, including azithromycin.[1,2,13] Most unilateral cases have been reported following administration of mitomycin or intracameral and topical moxifloxacin supporting a toxic etiology.[2,3,10–12] A strong association with antecedent upper respiratory tract infection raised consideration of an infectious etiology, particularly in patients who had not received antibiotics.[1,7,8] The causative infectious agent is not known. Anterior chamber PCR for herpes virus family is usually negative in the published cases of BAIT and BADI.[1,2,14] Our patient's clinical presentation with an acute onset of eye redness, irregular mid-dilated pupil, IPE necrosis with diffuse iris transillumination, absence of appreciable iris stromal depigmentation/atrophy, and prominent IPE pigmentary loss with pigment deposits in the trabecular meshwork associated with elevated intraocular pressure shortly following an upper respiratory tract/sinus infection and oral azithromycin were similar to what has been described in BAIT. However, unilateral presentation is exceptionally rare in this syndrome[8,9] and raises consideration of an alternative diagnosis.

Herpes virus infection of the eye can present with iritis, pigment dispersion, iris atrophy, and elevated intraocular pressure in the absence of keratitis.[15,16] However, the process in our patient was primarily restricted clinically to the IPE and sphincter muscle with no clinical evidence of iris stromal involvement. Although "iritis" was noted by the referring provider, the nature of the anterior chamber cells (pigmented vs. white blood cells) was not documented and the anterior chamber was quiet at the time of presentation to the Oncology Service. There was no evidence of inflammatory posterior synechiae formation. Additionally, herpetic iritis usually is accompanied by keratic precipitates, which were absent in our patient.[15] Similarly, the histopathologic findings of the enucleated globe are not conclusive of a herpetic etiology of the process. Histopathologically, the inflammatory infiltrate in the uveal tract was extremely mild, restricted to the iris root and the adjacent ciliary body, and predominantly lymphocytic in nature with scattered melanophages. There was no evidence of plasma cells, neutrophils, or

granulomatous inflammation that are frequently seen in herpes viral infection.[15,17] Histopathologically, the necrosis of the iris primarily was restricted to the IPE/dilator muscle complex and sphincter muscle. In addition, rare adjacent deep stromal vessels were affected and there was mild focal hypocellularity in the adjacent stroma, without overt stromal involvement. Although a vascular insult, as seen in our case, can be a feature of herpes virus infection, there was no evidence of active vasculitis. There were no nuclear viral cytopathic changes typical of herpes virus infection and immunohistochemical studies did not reveal herpes virus antigens. However, morphologic and immunohistochemical studies for herpes virus infection can be limited by sampling. Additionally, it is possible that topical corticosteroids administered to our patient could have modified the histopathologic findings. Finally, it is possible that both clinical and histopathologic findings in our patient might reflect early presentation of herpes virus infection before classic stigmata of HSV iritis develop. In our case, HSV-1 DNA was detected by the PCR performed on the paraffin-embedded tissue. Although PCR rarely can show a false-positive result in cases with HSV contamination, the combined clinical and histopathologic findings in our patient in the absence of any other identifiable cause supports a herpes viral etiology. Ideally, the diagnosis of herpes virus-associated iritis in this complicated case could have been supported by PCR on the anterior chamber fluid, but unfortunately, this study was not performed due to concern for melanoma. At the time of our patient's presentation in 2011, viral PCR on anterior chamber fluid was not as reliable or as widely accessible as it is currently.

Although not typical of herpes virus-associated iritis, our patient's presentation is reminiscent of the case reported in 2011 by Dastrup et al.,[18] describing a patient with unilateral iris transillumination and mostly pigmented cells in the anterior chamber, prominent pigment deposition in the anterior chamber angle, and elevated intraocular pressure of 48 mm Hg. Histopathologic evaluation of iris and corneal biopsies obtained at the time of trabeculectomy showed iris stromal atrophy without appreciable inflammation, similar to our findings. As seen in this case, neither iris nor corneal tissue were positive for HSV-1 by immunohistochemistry. Unlike our case, however, the patient reported by Dastrup et al. had keratic precipitates.[18] The macrophages in keratic precipitates showed nuclear HSV-1 positivity, while qualitative PCR on the anterior chamber fluid, iris, and corneal tissue for HSV-1, HSV-2, and VZV DNA yielded indeterminate results.[18]

Both our patient and the case reported by Dastrup et al.[18] highlight the unusual presentation of unilateral iris transillumination and depigmentation likely related to HSV-1 infection and the challenges of confirmatory immunohistochemical and molecular diagnostic studies. While the etiology of UAIT in our patient is not entirely clear, it is important to highlight that this process can simulate diffuse iris melanoma, underscoring the importance of careful clinical history and clinical correlation. Aqueous chamber tap for viral PCR in this setting could be informative.

4. Conclusion

In conclusion, unilateral iris transillumination with pigment dispersion can masquerade as iris melanoma. The history of antecedent upper respiratory tract infection and antibiotic use may suggest the diagnosis. HSV studies on aqueous fluid should be considered in this setting and may be diagnostic of an underlying HSV-related etiology.

Patient consent

Written consent to publish the case report was obtained. This report does not contain any personal information that could lead to the identification of the patient.

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Authorship

All authors attest that they meet the current ICMJE criteria for authorship.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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