

Brief Report

Bilateral acute depigmentation of the iris in two siblings simultaneously

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ABSTRACT

Purpose: To report the first simultaneous onset of bilateral acute depigmentation of the iris (BADI) in two siblings.

Observations: Two sisters presented with bilateral ocular pain, redness and light sensitivity. Examination revealed bilateral circulating pigment in the anterior chamber with pigment dusting on backs of the corneas, patchy iris depigmentation and heavy pigment deposition in the angle. Both patients had recently suffered from upper respiratory tract infections. Bilateral visual acuities were preserved and no transillumination defects were observed. The patients were diagnosed with BADI. Both cases were successfully controlled with topical corticosteroids and anti-glaucoma drops as well as topical glanciclovir gel.

Conclusions and Importance: To date, there had been no published reports of BADI in the Middle East and Africa. This is the first observation of this entity in these regions. Moreover it is the first occurrence of BADI in two immediate siblings simultaneously. We also report the rare asymmetrical presentation with BADI in one of our patients. These observations point to the possibility of genetic factors underlying BADI as well as an infectious cause behind the etiology.

1. Introduction

Bilateral acute depigmentation of the iris (BADI) is a newly described entity characterized by acute onset of depigmentation of the iris stroma.¹ Pigment often disperses into the anterior chamber and is deposited heavily in the anterior chamber angle. Clogging of the trabecular meshwork often results in increased intraocular pressure. Patients present with red eyes, photophobia, ocular discomfort and/or pain. BADI involvement is usually bilateral, symmetrical and most commonly occurs in young females in their third and fourth decades.^{1–3} Contrary to the closely related syndrome of bilateral acute iris transillumination (BAIT), BADI patients do not present with symptoms of transillumination and pupillary deformities.^{1,4} Cases of BADI and BAIT often occur after a flulike illness or upper respiratory tract infection. Moreover, several cases of BAIT have been associated with recent ingestion of oral moxifloxacin.^{5,6} Previous cases of BADI have been well controlled with topical corticosteroids, although in many cases corticosteroids lead to an increase in IOP.²

Since its initial characterization by Tukul-Tutkun et al., in 2005, fewer than 100 cases of both BADI and BAIT have been described worldwide: 51 in Turkey, 4 in the Netherlands, 4 in Belgium, 4 in Colombia, one in Spain, one in France and one in Brazil.^{1–3,7–9} To our knowledge, there are no previous reports of BADI cases in the Middle

East and Africa. Here, we present the first two cases of BADI in the region.

2. Case 1

A 28 year old female presented on October 1st, 2017 with acute severe bilateral ocular pain, light sensitivity and redness. Her best-corrected visual acuity (BCVA) was 1.0 in both eyes. Slit lamp examination revealed bilateral +2 ciliary injection, pigment clumps on the back of the corneas (Krukenberg spindles), +2 circulating pigment in the anterior chamber and symmetrical patchy depigmentation that was mostly close to the iris root, resulting in a more exaggerated appearance of the iris furrows. No transillumination defects were present (Fig. 1a–d). Pupils were rounded, regular and reactive. The lens was clear and posterior segment examination was unremarkable with no vitreous cells. Her intraocular pressures (IOPs) were 16 mmHg and 18 mmHg in the right and left eye, respectively. Gonioscopy revealed open angles with heavy pigmentation of the trabecular meshwork, especially in the inferior quadrant (Fig. 1e and f).

The review of systems was unremarkable apart from an upper respiratory tract infection one month prior to the onset of symptoms. It remains unknown whether the patient was treated with moxifloxacin.

The patient was immediately started on topical corticosteroids and

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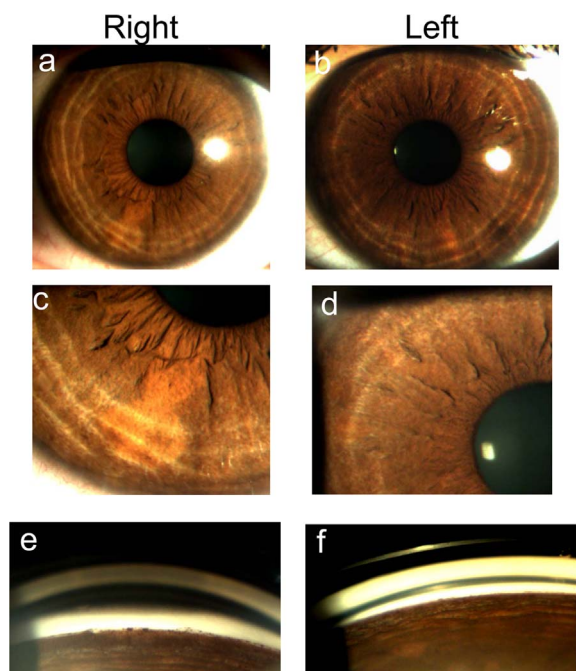


Fig. 1. Case 1. Slit-lamp photographs of Case 1, 28 year old female presenting with bilateral acute symmetrical iris depigmentation. Pictures were taken 7 weeks after initial presentation. 1a and 1b show right and left patchy peripheral geographic stromal atrophy respectively. 1c shows area of normal iris pigmentation surrounded on either side by areas of lost pigmentation in the patient's right eye. 1d shows peripheral patchy loss of pigmentation in left eye. 1e and 1f show gonioscopy of patient's heavily pigmented inferior angles due to pigment deposition.

cyclopentolate drops, which resulted in marked relief of symptoms and a decrease in circulating pigment in the anterior chamber to +1. Ten days after initial presentation, there was an increase in IOPs to 20 mmHg and 23 mmHg in the right and left eye, respectively. Any attempt to taper topical steroids early prior to the full resolution of pigment dispersion resulted in the recurrence of the initial symptoms. IOP remained persistently elevated at 23 mmHg. Topical anti-glaucoma was then prescribed to lower IOP.

Serological tests for herpetic viruses were all negative with the exception of highly positive CMV IgG count indicating a past CMV infection.

3. Case 2

A 25 year old female (the sister of Case 1) presented on October 4th 2017 with parallel symptoms of redness, pain and photophobia. Symptoms were more severe in the right eye. Her BCVA was 1.0 in both eyes. Slit lamp examination revealed bilateral +2 ciliary injection in the right eye and +1 in the left eye, pigment clumps on back of both corneas (Krukenberg spindles) that were more pronounced in the right eye, +3 circulating pigment in the right anterior chamber and +1 in the left eye, and symmetrical patchy depigmentation of the iris, mainly close to iris root. No transillumination defects were present (Fig. 2a–d). Pupils were rounded, regular and reactive. The lens was clear and posterior segment examination was unremarkable with no vitreous cells. Her IOPs were 16 mmHg and 22 mmHg in the right and left eyes, respectively. Gonioscopy revealed open angles with heavy pigmentation of the trabecular meshwork especially in the inferior quadrant, in addition to the presence of a fibrotic band on the back of the cornea in the inferotemporal quadrant of the right eye and nasal quadrant of the left eye. (Fig. 2 e,f).

Patient history included recurrent sinusitis with a recent exacerbation after an upper respiratory tract infection, which was treated with oral moxifloxacin in June.

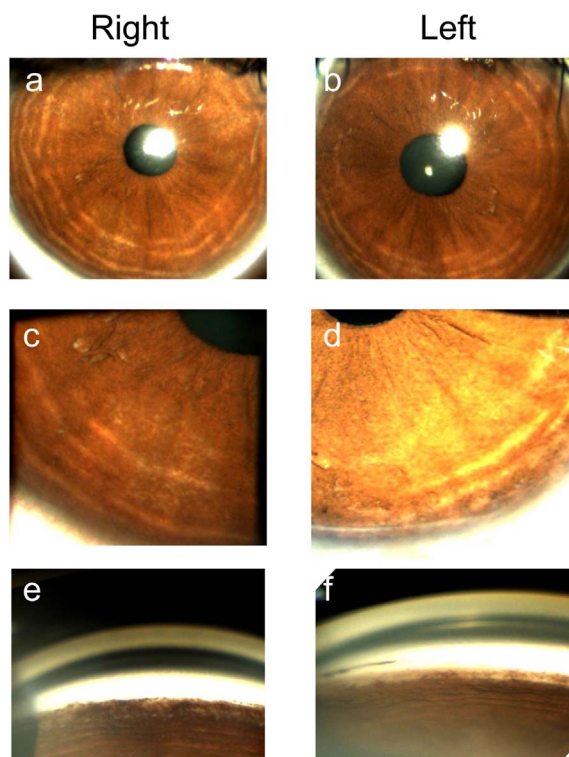


Fig. 2. Case 2. Slit-lamp photographs of Case 2, 25 year old female presenting with bilateral acute asymmetrical iris depigmentation. Pictures were taken 7 weeks after initial presentation. 2a and b show right and left patchy bands on the back of inferotemporal cornea in right eye and nasal cornea of left eye. Fig. 1c and d shows areas of normal iris pigmentation with peripheral areas of lost pigmentation in the patient's right and left eyes respectively. Fig. 1e shows gonioscopy of patient's heavily pigmented inferior angle of right eye due to pigment deposition. Fig. 1f shows nasal quadrant of left eye with pigmented line on back of peripheral cornea.

The patient was immediately started on topical corticosteroids and cyclopentolate drops, which alleviated pigment dispersion. Ten days later, the IOPs measured were 22 mmHg and 28 mmHg. Any attempt to quickly taper topical steroids to control IOP resulted in a flare with an increase in circulating pigment in anterior chamber. Topical anti-glaucoma was then prescribed to lower IOP.

Similar to Case 1, serology results were negative for herpetic viruses with the exception of highly positive CMV IgG counts. Seven days later, serology for CMV IgG count was repeated for both cases to find out if there is a rising titer for the antibodies. The results came back with the same numbers for both cases.

Both cases were prescribed the same treatment of cortical steroids and cyclopentolate drops. During the gradual tapering of topical steroids from six times daily, the amount of pigment dispersion decreased yet stabilized at +0.5 - +1.0 with no further improvement in both patients. At the stage of three times daily topical prednisolone acetate, topical ganciclovir 0.15% ophthalmic gel (trade name Ganvir, Orchidia Pharmaceuticals, Egypt) was prescribed five times daily. One week after the initial use of topical ganciclovir there was complete resolution of the pigment in the anterior chamber in both cases despite continuous topical steroid tapering. IOP returned to normal (Case 1 OD: 20, OS:18, Case 2: OD 17, OS:17) two weeks after anti-glaucoma treatments were halted.

During the course of the disease, the anterior chamber reaction and pattern of iris depigmentation were strikingly similar in the two siblings. Both patients had patchy stromal iris depigmentation, gradual rise in IOP (despite decreasing steroid drops frequency), minimal flare, and absolutely no signs of inflammatory keratic precipitates or transillumination iris defects. The only dissimilarity between the two cases was the symmetrical presentation in Case 1 and asymmetrical

presentation in Case 2. Interestingly, disease onset was almost simultaneous in both siblings and occurred after a recent upper respiratory tract infection. Moreover, both patients were positive for systemic past CMV infection.

4. Discussion

Bilateral acute depigmentation of the iris (BADI) is a rare but well documented form of pigment dispersion. Due to the large overlap in symptoms, BADI can often masquerade as uveitis or other pigment dispersion diseases, making further characterization by careful documentation of utmost importance.

When we first suspected BADI, it was necessary to rule out other diseases with similar presentations in order to tailor management according to the nature of the disease. Although herpetic iridocyclitis and BADI share many common symptoms such as patchy iris depigmentation and prior herpetic virus infection, the key difference lies in the unilateral involvement of herpetic iridocyclitis, its characteristic inflammatory keratic precipitates and full thickness patchy or sectoral stromal iris atrophy, which were not observed in our BADI patients.^{2,10} Fuch's heterochromic iridocyclitis also presents with iris depigmentation and atrophy, however it is most often unilateral with stellate keratic precipitates and a change in iris colour rather than complete loss of pigment.^{11,12} BADI can also potentially be mistaken for pigment dispersion syndrome.¹³ We excluded pigment dispersion syndrome in the cases presented here due to the lack of pigment deposition on the lens and zonules, forward iris concavity and chronicity. Moreover, pigment dispersion syndrome is more common in myopic males with an insidious onset and a more chronic course.^{13,14}

Case 1 represents a classic case of BADI with many of the previously described presentations and symptoms. A young 20–40 year old female is affected and presents with acute, bilateral, symmetrical and patchy iris depigmentation, without intraocular inflammation or full thickness iris atrophy. Case 2 is a less typical case of BADI, as presentation is asymmetrical and the symptoms are more pronounced in the right eye than the left. Although asymmetrical presentation is rare, it is not unprecedented and has been previously observed by Barraquer and Mejiain (2005) as well as Tugal-Tutkun in 2009.^{2,9} Although the patient does not recall suffering any trauma or previous ocular inflammation, we observed fibrous bands on the back of the cornea in Case 2, which maybe a result of an old trauma or inflammation of which the patient was unaware. In the two cases presented above, the patchy depigmentation was observed closer to the iris root rather than pupil. This pattern is similar to the geographic atrophy pattern observed in 10 of the 26 cases reported in the case series by Tugal-Tutkun et al. (2009).² Additional documentation of the patterns of depigmentation in BADI is required to understand the different patterns of depigmentation among patients presenting with BADI.

The etiology of BADI remains unknown, however, a viral etiology has been postulated by Tugal-Tutkun et al., in 2005 and 2009, where patients were reported to have suffered fevers or genital herpes shortly before to their presentation.^{1,2} Although systemic viral infection appears to have occurred, PCR testing of the aqueous tap was not positive for any of the herpetic viruses, rendering this hypothesis not yet proven. The two cases we present here reported a history of upper respiratory tract infection a few months prior to their symptoms of BADI. Although the causative organism of this infection remains unknown, it is important to note that both patients had highly positive CMV IgG antibodies, a serology similar to that of 10 of the 26 cases presented by Tugal-Tutkun et al., in 2009. As a result we hypothesize that BADI may have a viral etiology in these two cases. A positive PCR analysis for CMV on aqueous humour samples from these two patients would have supported this theory, however, viral PCR on aqueous tap samples is currently not available in Egypt.

During the course of follow-up, pigment dispersion had decreased and plateaued at +0.5–+1.0 in both patients for three weeks on topical

corticosteroids three times daily. At this point, ganciclovir therapy was started under the presumption of a viral etiology and resulted in the dramatic disappearance of pigment from the anterior chamber within one week. We are aware that topical antivirals are not usually used in the management of viral anterior uveitis, due to poor corneal penetration. However, topical ganciclovir 0.15% has demonstrated good corneoscleral penetration with the aqueous humour concentrations above the minimum inhibitory concentration required to treat herpetic anterior uveitis, in both animal and human models.¹⁵ Moreover, several groups have reported successful control of intraocular inflammation with topical valganciclovir 1% ointment after discontinuation of oral valganciclovir.^{16,17} Even though the response to topical ganciclovir was prompt, we cannot exclude that the complete resolution of pigment dispersion was due to the natural course of the disease.

Additionally, several recent reports have suggested a correlation between moxifloxacin and acute bilateral pseudouveitis. More specifically, cases of BAIT have been reported in patients shortly after completion of a moxifloxacin course.^{5,6} In these cases, moxifloxacin toxicity has been associated with severe pigment dispersion into the anterior chamber and full thickness stromal iris atrophy leading to transillumination defects. Toxicity to fluoroquinolone, from which moxifloxacin is derived, has been previously associated with bilateral uveitis in 40 patients.¹⁸ Ten of these patients underwent HLA typing and 4 were found to be HLA-B51 positive, suggesting a genetic tendency for fluoroquinolone toxicity. We suggested HLA typing to our patients, however, both refused to undergo any further testing. Therefore, it remains unknown, whether the observed symptoms are a result of predisposition to moxifloxacin toxicity. Although symptoms similar to those associated with moxifloxacin toxicity were observed in the two cases we present, we do not think this is the case here, as exposure to moxifloxacin occurred several months prior to patient presentation with BADI. Nonetheless, it is possible that moxifloxacin toxicity is milder in these two cases and has therefore caused less severe symptoms resulting in BADI rather than BAIT or a more aggressive form of uveitis.

The two cases presented here are the first report of BADI occurrence in the Middle East and Africa. Also, it is the first report to occur in 2 siblings simultaneously, leading us to speculate on the genetic basis of BADI. Other pigment dispersion diseases such as pigment dispersion syndrome (PDS) have been linked to a wide range of genetic mutations.^{19,20} This, together with the fact that most cases of BADI have been reported in Turkey, in proximal geographic regions (i.e. in individuals from the same gene pool) suggests that there may be genetic factors making some individuals more predisposed to developing BADI upon viral infection than others. Hence, identifying the mutations leading to BADI has become of great interest to us. Diseases of pigment dispersion appear to be inherited in a multifactorial fashion.²¹ This poses additional difficulties in the identification of the genes involved in BADI; however, it is reasonable to adopt a candidate gene approach beginning with genes already implicated in other pigment dispersion diseases. Understanding the genetic basis of BADI and continuing with diligent documentation of BADI cases will further aid in elucidating the pathology of this enigmatic disease.

5. Conclusion

Bilateral acute depigmentation of the iris is a rare and recent clinical entity in the field of glaucoma and uveitis. Because it is self-limited with good prognosis, it must be differentiated from other similar presentations of anterior uveitis. Even though the typical presentation of BADI is acute, bilateral and symmetrical, we observe a rare asymmetrical presentation of BADI symptoms in one of our patients. Corticosteroids and cyclopentolate drops followed by topical ganciclovir were prescribed and successful in disease management. Our patients are immediate siblings, who had recently suffered viral infections suggesting genetic factors underlying BADI as well as an infectious cause behind the

etiology, on which we must follow up to better understand the disease.

Patient consent

Written and informed consent was obtained from both patients for publication of these case reports and any accompanying images.

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Conflicts of interest

The following authors have no financial disclosures: R.H., A.N., N.K.

Authorship

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

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