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Iris pigment epithelial (IPE) cysts secondary to Hodgkin's lymphoma: A case report

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ABSTRACT

Purpose: To describe a unique case of a white male who presented with reduced visual acuity, growing bilateral iris pigment epithelial (IPE) cysts and granulomatous panuveitis, probably related to Hodgkin's lymphoma.
Observations: The granulomatous panuveitis was reactive to corticosteroids, but the IPE cysts were not. After extensive work-up, the patient was diagnosed with Hodgkin's lymphoma (HL) mixed cellularity type with cervical and mediastinal lymph node involvement. After starting chemotherapy, the IPE cysts shrank.
Conclusions and importance: To our knowledge, IPE cysts have not been described in HL before. Therefore, this case can contribute to our knowledge of the relation between IPE cysts and hematological malignancy.

1. Introduction

Iris cysts are reported in various occasions. Primary iris cysts of neuro-epithelial origin, can be congenital or acquired and seldom cause complications when enlarging. Iris cysts can also originate from underlying causes such as drugs, systemic disorders, parasites, tumors and uveitis, and are then called 'secondary'. The latter have a tendency to cause complications which can range from decrease in visual acuity to glaucoma or uveitis.[1–3] Imaging is often necessary for diagnosis and is preferably performed by ultrasound biomicroscopy (UBM) which has sufficient tissue penetration and excellent resolution. If iris cysts become symptomatic, treatment can be warranted.[1–3]

We report a unique case of an immunocompetent white male who presented with reduced visual acuity, granulomatous panuveitis and iris pigment epithelial (IPE) cysts. Eventually, he was diagnosed with Hodgkin's lymphoma (HL). The IPE cysts responded well to systemic treatment for his malignancy. To our knowledge, this is an atypical presentation that has not been reported in literature before.

2. Case report

A 62-year-old male patient presented at our ophthalmology department complaining of blurred vision especially in the right eye. His medical history was unremarkable besides suffering from asthma as a child and a bilateral pneumonia two years ago. He has been smoking 6 cigarettes a day for 30 years. He had already undergone a refractive clear lens extraction with implantation of a multifocal intra-ocular lens. On examination, the visual acuity was Snellen 20/32 and 20/20, respectively on the right and left eye. Biomicroscopy showed iridocorneal touch especially on the temporal sides due to IPE cysts in both eyes. There was a granulomatous panuveitis with anterior chamber cells 1+, keratic precipitates and swollen optic discs with mild vitritis but no retinitis. The eye pressure was within normal limits. The multifocal implant lenses were clear. He reported to have night sweats for a couple of months, but no other systemic symptoms, especially no weight loss. He was not on any medication currently. He was started on topical steroid (Prednisolone acetate in tapering scheme with one drop every week starting from six times a day) and a complete uveitic work up was performed. His serologic tests were negative for *Treponema pallidum* and Borrelia burgdorferi as well as Hepatitis B and C and Human immunodeficiency virus (HIV), but showed a positive Immuneglobuline (Ig) G for Epstein Barr Virus (EBV). Computed Tomography (CT) of the chest with contrast enhancement showed swollen mediastinal lymph nodes suggestive of sarcoidosis. Angiotensin-Converting Enzyme (ACE) was 41 U/L and Calcium 2.29 mmol/L, both within normal range. However, his tuberculin skin test and consequently Interferon Gamma Release Assay

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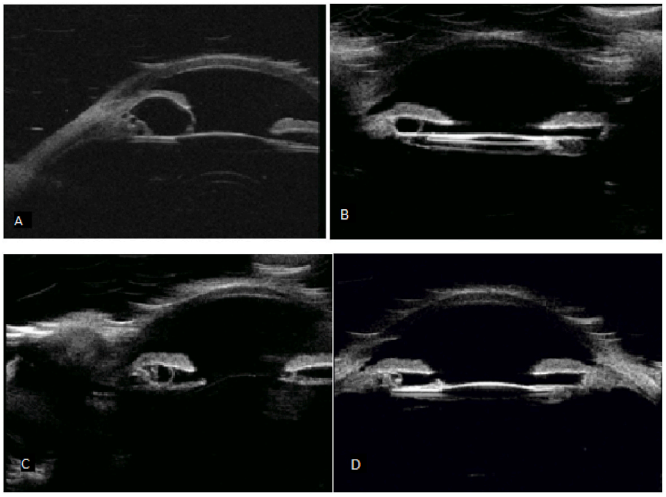
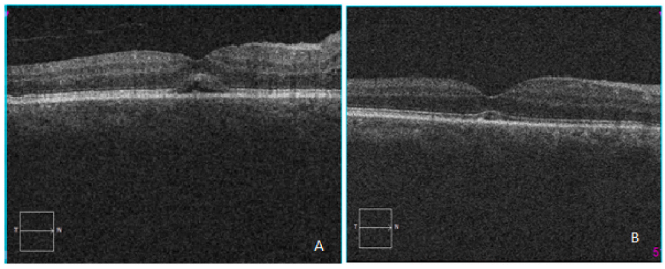
(IGRA) came back positive. To cover for latent tuberculosis, he was started on anti-tuberculosis therapy with Isoniazide, as well as oral steroids (Methylprednisolone 64mg in following tapering scheme: 64 mg and 48mg each for 5 days, then 32 mg–28 mg −16 mg–8 mg – 4 mg each for one week). The intraocular inflammation and swelling of the optic discs decreased and his vision improved to Snellen 20/25 in the right eye, the left eye remained 20/20. However, the iridocorneal touch on the temporal sides persisted.

When the oral steroids were completely tapered, the blurred vision reoccurred. An increase in optic disc swelling, as well as an increase in IPE cysts and a relapse of granulomatous panuveitis was noted. (Figure 1A and C) He also suffered from a myopic shift (from −0.75D to −4.50D automated refraction (NIDEK)) especially on the right side, caused by increased swelling of the IPE cysts with posterior displacement of the IOL. Optical Coherence Tomography (OCT, Cirrus, Zeiss) showed a new finding of macular vitelliform deposits and a small collection of subretinal fluid in the right eye (Picture 2A). Also, other vitelliform autofluorescent lesions developed supratemporal of the fovea in both eyes (Picture 3). He was restarted on oral steroids with regression of optic disc swelling and subretinal fluid, but no response on the IPE cysts. An anterior chamber tap was not performed due to the very limited space within the anterior chamber caused by the IPE cysts. The patient was sent to our pneumology department for further systemic investigation and biopsy with endoscopic biopsy ultrasound (EBUS) of the swollen lymph nodes, seen on CT of the chest. Histopathological examination of these lymph nodes was negative for sarcoidosis and tuberculosis. Subsequent PET-CT scan showed an increased signal at a cervical lymph node, that was resected. This lymph node was positive for an EBV driven inflammation but pathology and immunohistochemistry could not differentiate between a classic Hodgkin lymphoma, Epstein-Barr virus (EBV) driven B-cell lymphoma or active EBV infection. Eventually, with copy number variation (CNV) sequencing on cell free DNA the diagnosis of a classic Hodgkin lymphoma, mixed cellularity type, could be made.

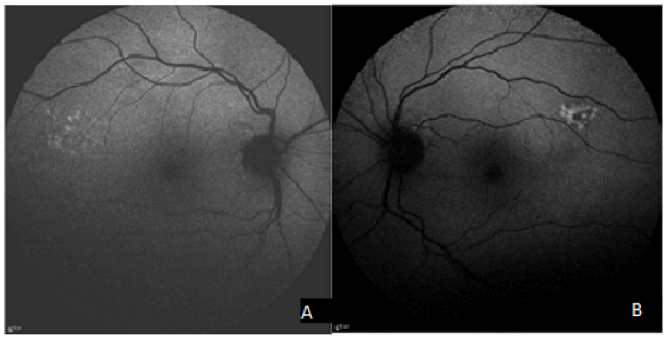
Six weeks after the diagnosis, respectively five months after the initial presentation in our ophthalmology department, corticosteroids were stopped again and the patient was started on chemotherapy (Adriamycine, Bleomycine, Vinblastine and Dacarbazine (ABVD)). With this treatment, the IPE cysts shrank clearly (Picture 1B and 1D). OCT of the macula showed a small amount of residual subretinal fluid and



Picture 1. Ultrasound biomicroscopy (UBM) images of the IPE cysts.
A: Right eye before initiating chemotherapy. The IPE cysts are quite large and clearly visible between lens and iris B: Great reduction in size of the IPE cysts in the right eye six weeks after starting chemotherapy. C: Left eye before chemotherapy with some smaller cysts visible between iris and lens. D: Left eye after initiating chemotherapy with decrease in cyst size.



Picture 2. Optical Coherence Tomography (OCT) of the macula right eye.
A: OCT of the right eye with deposit of subretinal vitelliform material as well as subretinal fluid. On the left side of the image, the swollen disc is also visible. B: A small amount of subretinal fluid remains after starting chemotherapy.



Picture 3. Auto-fluorescence images of respectively the right
(A) and left eye (B) which shows hyperautofluorescent vitelliform deposits superotemporal of the fovea, that were not present at first presentation.

vitelliform material in the right eye (Picture 2B). The vision improved again and the refraction error diminished significantly (from −4.50D to −1.00D automated refraction (NIDEK)).

3. Discussion

Ocular involvement secondary to Hodgkin lymphoma has been described but is uncommon and is mainly reported with diagnostic or therapeutic delay.[4] Hodgkin's lymphoma can be associated with a granulomatous panuveitis. However, to our knowledge, there are no previous papers reporting the presence of IPE cysts, although Towler et al. described one case with granulomatous iris nodules.[4–9]

It is thought that ocular inflammation secondary to Hodgkin's lymphoma is caused by a tumor-driven auto-immune reaction to non-tumor cells or a tissue response to an underlying stimulus, e.g. EBV.[4,10] Although the exact immune process is not yet completely understood and seems to be very complex, there might be a role for Cluster of Differentiation (CD) 30 cells. CD30 expressing cells are present in the normal eye and have an immune suppressive function by limiting proliferation of auto-reactive CD8 effector T-cells.[11] Hodgkin's lymphoma is known to express a high amount of CD30, but different mitogens and viruses, such as EBV, can also upregulate CD30.[11–13] As the innate and adaptive immune system of the patient try to conquer the tumor, this might be accompanied with an immune response not only to CD30 positive cells expressed by the tumor, but also to other CD30 positive cells, for example in the eye. An immune response to CD30 might lead to proteolytic cleavage with increased concentration of soluble (s)CD30, leading to more auto-immunity and proliferation of autoreactive effector T-cells due to the loss of the protective function of these CD30 cells.[11] Moreover, CD30 might also contribute to the inflammatory process in granulomatous uveitis, as higher concentrations of sCD30 are described in anterior chamber samples of patients with active granulomatous uveitis.[14,15] It can be hypothesized that due to this increase in

CD30 expression, either upregulated by the carcinogenic EBV infection or due to his asthmatic condition, there might be an increased level of CD30 positive cells in different tissues, including the uvea (e.g. iris and choroid).

Another hypothesis supports the role for paraneoplastic anti-tumor antibodies that cross react with ocular tissues by means of molecular mimicry. This is called "Lymphoma Associated Retinopathy", as a form of Carcinoma Associated Retinopathy (CAR).[5] For example, some papers describe an anti-retina specific antibody associated with Hodgkin's disease.[5,7,8] Regardless of the hypothesis, these reactions result in an auto-immune phenomenon, which can explain a granulomatous panuveitis as was seen here. Typically this auto-immune reaction responds to corticosteroids, but can recur after tapering, if the inciting tumor is not treated, as was seen in our case.

Interestingly, the patient also developed some vitelliform lesions throughout the course after tapering the corticosteroids, that were not present at presentation. This might reflect an immune reaction directed to the Retinal Pigment Epithelium (RPE), as is described in Paraneoplastic Vitelliform Retinopathy or Paraneoplastic Acute Exudative Polymorphous Vitelliform Maculopathy (pAEPVM).[9,16] This condition is mostly described in melanoma, but can be found in other tumors as well. It is characterized by scattered vitelliform lesions, often associated with serous retinal detachments and accumulation of lipofuscin-rich material, leading to hyperautofluorescence. This accumulation of lipofuscin rich fluid is probably caused by dysfunction of the RPE, with decreased phagocytosis of photoreceptor outer segments and reduced pumping function of the RPE.[9,16,17] In literature there is no convincing evidence for the use of corticosteroids in this condition.[18,19]

The iris cysts in this case seem to originate from the Iris Pigment Epithelium (IPE), as they are found on the posterior side of the iris. The IPE has the same embryological origin as the RPE and has some features that resemble the RPE. Both are highly pigmented layers that have a pumping function.[20] Therefore it is not unthinkable that the vitelliform lesions and the iris cysts are caused by the same immune reaction, leading to an attenuated function of both RPE and IPE. This might also explain the lack of response to corticosteroids of both vitelliform lesions and iris cysts, as the function of the RPE and IPE cannot recover instantly, unlike the uveitis.[20] Furthermore, the function probably cannot restore if the inciting tumor immune reaction is still present, left aside if it is CD30 related or antibody related. It was also only after resection of the cervical lymph node and starting chemotherapy, that the IPE cysts shrank. We can assume that this intervention caused a decrease in the immune response against the tumor and secondary a decrease in the reaction against the eye.

It is possible that the IPE cysts were already present in this patient and never have been diagnosed before. However, it seems that these IPE cysts have changed in size during the course of the disease, given that the patient clearly myopized (he was emmetropic after his clear lens extraction) possibly caused by the growth of these cysts, with subsequent posterior displacement of the IOL, and the new presence of iridocorneal touch. Only after resection of the cervical lymph node and initiating chemotherapy, the iridocorneal touch resolved and the refractive error diminished (from −4.25 to −1.00, automated refraction (NIDEK)). This supports the hypothesis that the new presence or growth of the IPE cysts could be related to a tumor-driven process as they responded well to chemotherapy.

There are two possible explanations for the limited reporting in literature about IPE cysts secondary to Hodgkin's lymphoma. First, this can be a rare entity. Second, there could be a major underreporting due to difficulties visualizing these IPE cysts during slit lamp examination. Often, investigation with Optical Coherence Tomography (OCT) of the anterior segment or Ultrasound biomicroscopy (UBM) are necessary for imaging. Further research is necessary to clarify the pathogenesis of IPE cysts and their prevalence in patients with Hodgkin lymphoma as well as malignancy in general.

4. Conclusion

Iris cysts are not an infrequent finding and can be primary or secondary in origin. We reported a case of a patient who presented with IPE cysts which did not respond to oral steroids but shrank after initiating chemotherapy for Hodgkin's lymphoma. We can conclude that the cysts were probably linked to the lymphoma. To our knowledge, there is no similar case in literature. Further research is necessary to investigate the prevalence of IPE cysts in patients with Hodgkin's lymphoma and to clarify the pathogenesis of these cysts in malignancy.

Patient consent

The study and data accumulation were carried out with approval from the appropriate Institutional Review Board (IRB) and Informed Consent was obtained from the patient.

Declaration of interests

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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References

1. Georgalas I, Petrou P, Papaconstantinou D, Brouzas D, Koutsandrea C, Kanakis M. Iris cysts: a comprehensive review on diagnosis and treatment. *Surv Ophthalmol*. May-Jun 2018;63(3):347–364. https://doi.org/10.1016/j.survophthal.2017.08.009.
2. Rao A, Gupta V, Bhadange Y, Sharma R, Shields JA. Iris cysts: a review. *Semin Ophthalmol*. Jan 2011;26(1):11–22. https://doi.org/10.3109/08820538.2010.541319.
3. Lois N, Shields CL, Shields JA, Mercado G. Primary cysts of the iris pigment epithelium. Clinical features and natural course in 234 patients. *Ophthalmology*. Oct 1998;105(10):1879–1885. https://doi.org/10.1016/s0161-6420(98)91034-x.
4. Towler H, de la Fuente M, Lightman S. Posterior uveitis in Hodgkin's disease. *Aust N Z J Ophthalmol*. Oct 1999;27(5):326–330. https://doi.org/10.1046/j.1440-1606.1999.00224.x.
5. To KW, Thirkill CE, Jakobiec FA, Lessell S, Berson EL. Lymphoma-associated retinopathy. *Ophthalmology*. Nov 2002;109(11):2149–2153. https://doi.org/10.1016/s0161-6420(02)01261-7.
6. Mosteller MW, Margo CE, Hesse RJ. Hodgkin's disease and granulomatous uveitis. *Ann Ophthalmol*. Dec 1985;17(12):787–790.
7. Ohta K, Yoshida A, Sato A, Fukui E, Kikuchi T. Retinal involvement in uveitis associated with Hodgkin disease. *Retin Cases Brief Rep*. 2014;8(1):17–20. https://doi.org/10.1097/ICB.0b013e3182a489f1.
8. Dedieu D, Bouayed E, Brézin AP. Hodgkin lymphoma associated retinopathy: report of a case. *Ocul Immunol Inflamm*. May 13 2021:1–3. https://doi.org/10.1080/09273948.2021.1912360.
9. Alshamrani AA, Alsarhani WK, Aljasser AA, Rubio-Caso MJ. Granulomatous panuveitis associated with Hodgkin lymphoma: a case report with review of the literature. *Eur J Ophthalmol*. Nov 5 2020. https://doi.org/10.1177/1120672120969036, 1120672120969036.
10. Ayhan Z, Yıldırım Karabağ R, Alacacıoğlu İ, Kaynak S, Koçak N. Rare clinical sign of hodgkin's lymphoma: ocular involvement. *Turk J Ophthalmol*. Apr 2017;47(2):110–112. https://doi.org/10.4274/tjo.92609.
11. Kennedy MK, Willis CR, Armitage RJ. Deciphering CD30 ligand biology and its role in humoral immunity. *Immunology*. Jun 2006;118(2):143–152. https://doi.org/10.1111/j.1365-2567.2006.02354.x.
12. van der Weyden CA, Pileri SA, Feldman AL, Whisstock J, Prince HM. Understanding CD30 biology and therapeutic targeting: a historical perspective providing insight into future directions. *Blood Cancer J*. Sep 8 2017;7(9), e603. https://doi.org/10.1038/bcj.2017.85.
13. Shannon-Lowe C, Rickinson AB, Bell AI. Epstein-Barr virus-associated lymphomas. *Philos Trans R Soc Lond B Biol Sci*. Oct 19 2017;(1732):372. https://doi.org/10.1098/rstb.2016.0271.
14. Abu El-Asrar AM, Berghmans N, Al-Obeidan SA, et al. Soluble cytokine receptor levels in aqueous humour of patients with specific autoimmune uveitic entities: sCD30 is a biomarker of granulomatous uveitis. *Eye*. Sep 2020;34(9):1614–1623. https://doi.org/10.1038/s41433-019-0693-7.
15. Rojas-Ramos E, Garfias Y, Jiménez-Martínez Mdel C, et al. Increased expression of CD30 and CD57 molecules on CD4(+) T cells from children with atopic asthma: a preliminary report. *Allergy Asthma Proc*. Nov-Dec 2007;28(6):659–666. https://doi.org/10.2500/aap.2007.28.3057.

16. Przeździecka-Dołyk J, Brzecka A, Ejma M, et al. Ocular paraneoplastic syndromes. *Biomedicines*. Nov 10 2020;8(11). https://doi.org/10.3390/biomedicines8110490.
17. Aronow ME, Adamus G, Abu-Asab M, et al. Paraneoplastic vitelliform retinopathy: clinicopathologic correlation and review of the literature. *Surv Ophthalmol*. Nov 2012;57(6):558–564. https://doi.org/10.1016/j.survophthal.2012.02.004.
18. Grenga PL, Fragiotta S, Cutini A, Vingolo EM. Acute exudative polymorphous vitelliform maculopathy: to bolus or not to bolus? *Oman J Ophthalmol*. 2018;3:280–283.
19. Scupola A, Abed E, Sammarco MG, et al. Intravitreal dexamethasone implant for acute exudative polymorphous vitelliform maculopathy. *Eur J Ophthalmol*. Sep-Oct 2014;24(5):803–807. https://doi.org/10.5301/ejo.5000477.
20. Thumann G. Development and cellular functions of the iris pigment epithelium. *Surv Ophthalmol*. Jan-Feb 2001;45(4):345–354. https://doi.org/10.1016/s0039-6257(00)00195-8.