Isolated intraocular histiocytosis—A rarely reported entity masquerading clinically as uveitis

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An immunocompetent, 25-year-old gentleman with bilateral chronic uveitis presented to various uveitis clinics at different points of time with documented typical clinical features of Toxoplasma Chorioretinitis (Headlight in fog appearance), Behcet’s Disease (Hypopyon with peripheral retinal vasculitis), and Presumed Ocular Tuberculosis (Granulomatous Intermediate Uveitis with positive Interferon-gamma release assay) and had been treated with anti-toxoplasma drugs, oral prednisolone, and immunomodulation with oral Mycophenolate/oral Azathioprine to no avail. After cytological examination of vitreous aspirate, he was found to have non-Langerhans cell Histiocytosis which responded to chemotherapy with Vinblastine and Cyclophosphamide.

Key words: Intraocular histiocytosis, non-langerhans histiocytosis, uveitis masquerades

“Intraocular Histiocytosis” is a very rarely reported entity; with isolated case reports in literature and masquerades as “Hypopyon Uveitis” and presents with clinical features typical of other common forms of uveitis. It may be steroid responsive; but relapsing and requires intervention and treatment with an oncologist to achieve control of disease activity.

Case Report

An immunocompetent, 25-year-old gentleman with bilateral chronic uveitis presented to various uveitis clinics over 2 years at different points of time with typical clinical features of Toxoplasma Chorioretinitis (Headlight in fog appearance), Behcet’s disease (Hypopyon with peripheral retinal vasculitis); Presumed Ocular Tuberculosis (Granulomatous intermediate uveitis with positive Interferon-gamma release assay).

He had been extensively investigated prior to presentation with us (complete blood count with Erythrocyte Sedimentation Rate, Mantoux test, Serum Angiotensin Converting Enzyme, TORCH titers, HLA B5, HLA B51, Anti-nuclear antibody, Antineutrophil cytoplasmic antibody, MRI Brain with Orbit - All inconclusive) and treated with anti-Toxoplasma drugs, oral prednisolone, and immunomodulation variously with oral Mycophenolate/oral Azathioprine to no avail.

On presentation with us; he had best corrected visual acuity of 20/20, N6 in right eye with intraocular pressure of 14 mm Hg and 20/60 in left eye with posterior subcapsular cataract and an intraocular pressure of 16 mm Hg with sloping optic nerve rims. He had vitreous cells in both eyes (left more than right) with vitritis and cystoid macular edema in the left eye. The clinical picture on presentation to us was of Intermediate Uveitis in both eyes (left eye more than right eye) and being most commensurate with presumed ocular tuberculosis (normal High-Resolution CT Scan of the Chest done as requested by us and with a previously positive Interferon-gamma release assay); treatment with anti-tuberculosis drugs (AKT) was started; with only a partial response to treatment and relapses while tapering oral Prednisolone.

After 4 months of AKT with multiple relapses; the clinical picture changed with some relapses mimicking Ocular Toxoplasmosis [Fig. 1a and b] (Headlight in fog appearance); and a need for a vitreous biopsy was felt. Cytology smears and cell block from an undiluted vitreous sample obtained by vitreous biopsy and transported immediately to the laboratory for histological examination. Histological examination revealed granulomatous inflammation with intermediate uveitis and histiocytosis. The patient was started on systemic Cyclophosphamide, and his vision improved.

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showed Histiocyte predominance on microscopy [Fig. 1c]. These histiocytes were confirmed to be of non-Langerhans type by immunohistochemistry with CD 68 highlighting Histiocytes, and CD 1a and S-100 protein not expressed. Microbiology sampling of the vitreous showed no organisms on microscopy (Grams Stain and KOH Mount), no growth on bacterial (Nutrient Broth) and fungal (Sabouraud Dextrose Broth) cultures. The Xpert MTB/RIF which detects DNA sequences specific for Mycobacterium tuberculosis and rifampicin resistance by polymerase chain reaction was negative.

Patient was screened by an oncologist who ruled out other organ involvement by a systemic clinical examination, X-Ray of the skull, cervical spine, dorsal spine, lumbosacral spine, pelvis, a Te-MDP Bone scan, Contrast Enhanced CT Scan of the chest, abdomen and pelvis and with normal liver and renal function tests and Lactate Dehydrogenase levels. He was put on chemotherapy with injection Vinblastine over 3 months with a good response with disease activity relenting [Fig. 1d] to only 1+ vitreous cells and no vitritis in both eyes with a best corrected visual acuity of 20/20 in right eye and 20/60 in left eye with posterior subcapsular cataracts in both eyes; allowing taper of oral steroids to 2.5 mg alternate day within 6 months.

In the course of his treatment, he developed raised intraocular pressures in both eyes with associated glaucomatous disc changes in the left eye which were treated medically. Because there was no associated rise in intraocular inflammation and no peripheral anterior synchiae; this bilateral rise in intraocular pressure was considered to be induced by use of oral and topical steroids; as he had not been treated with any periocular or intraocular steroids. Six months on 2.5 mg of Prednisolone alternate day, he developed a rhegmatogenous retinal detachment with an inferotemporal horse-shoe tear in the left eye which required vitrectomy with silicon oil injection. The patient was not a myope and had no other risk factors for a retinal detachment. Within 1-month post-surgery, inflammation again became unstable in both eyes which was treated with oral steroids. In the next 8 months, he had migration of silicon oil in the anterior chamber and secondary uncontrolled intraocular pressures with a cataract in the left eye which necessitated cataract extraction with PCIOL implantation with silicon oil removal and later trabeculectomy with Mitomycin C to stabilize intraocular pressure. Further reactivations were attempted to be controlled initially with 35 mg of oral methotrexate per week as per oncologist for 10 weeks and later with pulsed IV Cyclophosphamide 750 mg. Six such pulses over 6 months achieved good control of inflammation. This was followed up with six 3-monthly pulses of IV Cyclophosphamide 750 mg with self-limiting minor peripheral reactivations.

At last follow-up; being 22 months in quiescence with 3.75 mg of oral prednisolone per day, he maintains a best corrected visual acuity of 20/20, N6 in right eye with an intraocular pressure of 10 mm Hg and CF at 3 meter in the left eye with an intraocular pressure of 10 mm Hg on combination of Timolol Maleate and Brimonidine with Brinzolamide eye drops with a visually significant posterior capsular opacification and foveal retinal thinning in addition to a glaucomatotic optic nerve cupping being the cause of loss of best corrected visual acuity.

**Discussion**

“Intraocular Histiocytosis” is a rare clinical entity[1,2] which masquerades as “Hypopyon Uveitis” and clinical features typical of other forms of uveitis.

Histiocytosis in the form of either Langerhans cell histiocytosis or non-Langerhans cell histiocytosis, is characterized by histiocyte proliferation and may involve various organs and tissues. Among lesions in other organs, characterized by skin disorders, lymphadenopathy, bone lesions, hepatosplenomegaly, lung disease and central nervous system lesions; the eyeball with its adnexa may also be affected, as is the case in Juvenile Xanthogranuloma, Rosai-Dorfman disease or Letterer-Siwe disease.

This rare entity of Intraocular Histiocytosis in an isolated form without systemic disease has been reported rarely in literature. A previously reported case is of a 12-year-old girl[3] who was additionally HLA B 51 positive and had Langerhans Cell Histiocytosis (LCH) unlike our patient who was HLA B 51 negative and had non-Langerhans Cell Histiocytosis. Another patient, a 49-year-old gentleman with choroidal Langerhans cell histiocytosis and no evidence of systemic lesions has also been previously reported.[4] He had been diagnosed to have choroidal melanoma based on clinical studies and angiographic findings and underwent enucleation of his right eyeball with immunohistochemical studies including S-100 and CD 68 staining showing characteristic features of Langerhans’ cell histiocytosis. In literature, the other reported patients had systemic involvement; one with hemorrhagic uveitis and systemic involvement[5] and other with unilateral anterior segment inflammation and iris nodule where the bone marrow aspirate confirmed recurrent, active LCH previously called Histiocytosis X.[5] Isolated Ocular Rosai-Dorfman Disease has also been recently reported[6] to present as a solitary choroidal mass with clinical features overlapping with a Uveal Melanoma.

**Conclusion**

The take home message from these cases would be that knowledge of this entity is important to any ophthalmologist. Our patient requiring treatment over 8 years and his follow-up over 5 years with us emphasizes; the all-important need for an initial through review of the clinical reports of all previous treating clinicians on first presentation as the same uveitis entity may have presented to various clinics in various different clinical patterns.

Further this entity is steroid responsive but relapsing on steroid taper. Cytological examination of the vitreous sample with immunohistochemistry as a diagnostic modality is of paramount importance. Treatment by an oncologist using chemotherapeutic agents to achieve control of disease activity would help us have better visual outcomes.

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**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other
clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**
There are no conflicts of interest.

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