

## BIRDSHOT RETINOCHOROIDOPATHY

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### ABSTRACT

**Purpose and Methods:** Birdshot Retinochoroidopathy is a chronic intraocular inflammatory disease affecting mainly the posterior segment of the eye. It is distinct from other forms of posterior uveitis because of a very characteristic clinical presentation and a strong association with HLA - A29.2 antigen. We present the saga of a patient whose initial presentation was atypical. Continued follow up and carefully tailored laboratory work established the diagnosis. **Conclusion:** This case illustrates the importance of continued follow up of patients with chronic inflammatory ocular disease in order to establish the definitive diagnosis and institute appropriate therapy.

### Case

A 45 year old white female was referred on February 27, 1992 by her primary ophthalmologist for a five months history of floaters and peripheral visual disturbances in both eyes. She also complained that colors appear washed out with her right eye.

Review of system was significant for Raynaud's phenomenon in her toes and occasional ear lobe pain. Past medical history was positive for Irritable Bowel Syndrome and Rosacea. Family history was significant for gout and diabetes mellitus. She was allergic to Bactrim and Keflex and was taking Tetracycline 200mg per day for her Rosacea.

Examination revealed visual acuity of 20/30 in both eyes and intraocular pressure was 11 and 14 mmHg in the right and left eye, respectively. Pupils showed no relative afferent defect & extraocular motility was full in both the eyes. Desaturation for red color (25-50 %) was present in her right eye. She had typical Rosacea facies. The anterior segment examination was within normal limits except for moderate blepharitis. Slit lamp biomicroscopy of the vitreous showed 2+ cells in the right eye and 1+ cells in the left eye.

Dilated fundus examination showed markedly attenuated arteries in both eyes and clumps of cells in the posterior vitreous. Optic disc margins were fuzzy, more so in right eye than the left eye.

The initial impression was:

Optic nerve dysfunction in right the eye with vitritis in both eyes

The plan was to obtain Neuro-ophthalmology consultation and visual field testing and fluorescein angiography (FA).

In March, 1992 the patient returned with a complaint of dim vision in the left eye. On examination her visual acuity was 20/25 in both eyes. The Rest of the examination was unremarkable except for 1+ cells in the vitreous in both the eyes. FA showed mild disc staining and leakage around vessels in both eyes. Visual Field examination showed scattered defects in both eyes. Neuro-ophthalmology examination was within normal limits including a CT scan of the head.

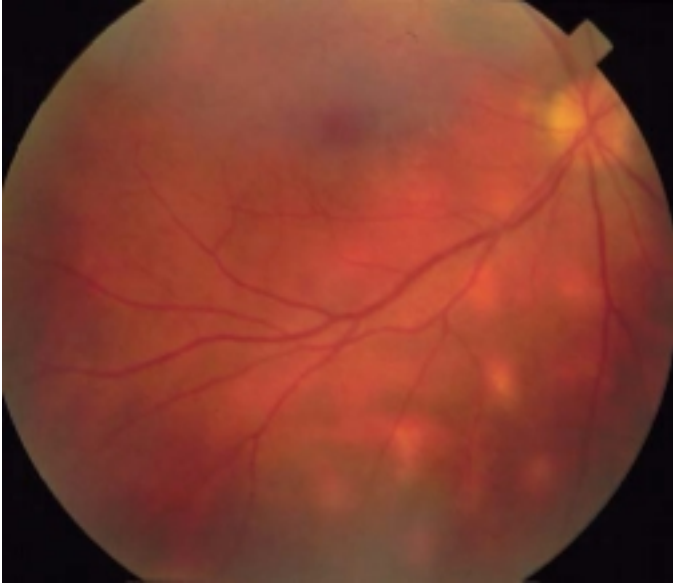
Laboratory investigations, consisting of CBC, Urine analysis, ANA, ANCA, ACE, Lysozyme, FTA-ABS, C1q and Raji cell assay, Anticardiolipin antibodies, HLA-B27 typing and Lyme Antibody titer were obtained. These proved to be unremarkable except for elevated Raji cell assay and positive Anticardiolipin antibodies.

The patient was advised to take an Aspirin daily because of the anticardiolipin antibodies.

Since her objective clinical status had remained stable, she continued to follow up with her local ophthalmologist.

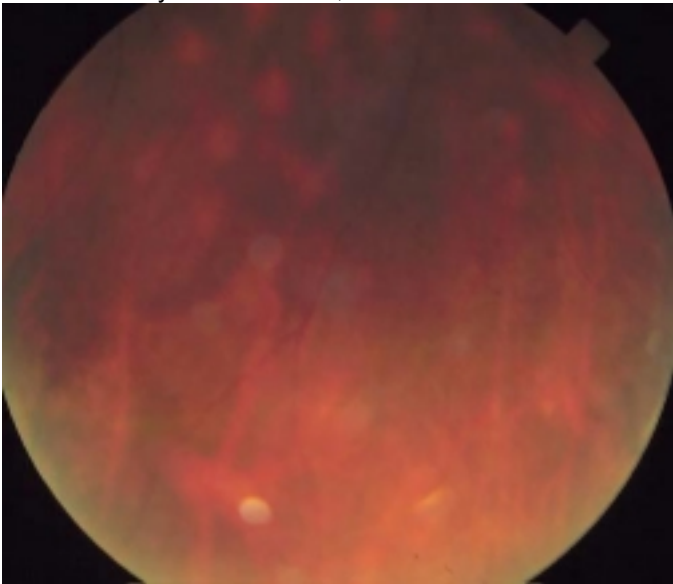
A year later in February, 1993, her primary ophthalmologist noted new lesions in the fundus, for which he again referred the patient to the Immunology service for further evaluation and management.

The patient's visual acuity was 20/20 in both eyes. The anterior segments were within normal limits. The vitreous showed 1+ cells in both eyes.



Fundus OD:

You can see yellowish-white, ill defined lesion inferior to inferior vascular arcade.



Fundus OS:

Similar lesions were noted in her left fundus as well.

In summary we have a 40 year old white female with over one year history of floaters, disturbances in color vision and peripheral field disturbances in both eyes. Anterior segment examination has been within normal limits. FA showed leakage around blood vessels and staining of disc in both eyes. Laboratory work up was negative, including MRI, LP and neuro-ophthalmic exam. Review of system was negative except Raynaud's phenomenon in her toes.

### **Differential Diagnosis**

Birdshot Retinochoroidopathy  
APMPPE  
MEWDS  
Multifocal Choroiditis  
Pars Planitis

So we have a healthy 40 years white female who presented with bilateral vitritis, retinal vasculitis, in absence of anterior segment inflammation with the distinctive fundus lesions of "Birdshot Retinochoroidopathy". The patient was HLA-A29 positive.

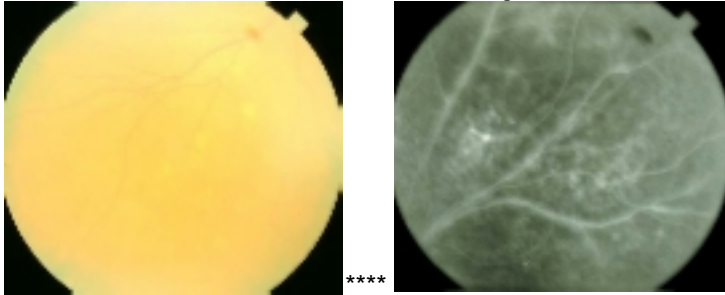
#### CLINICAL COURSE

The patient was started on Cyclosporine- A 200mg/day with a plan to continue therapy for at least one year.

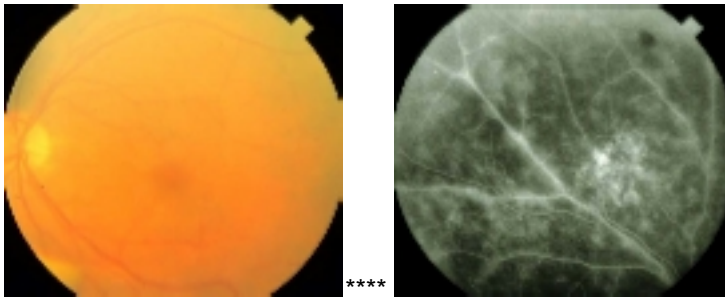
A year later in November, 1994, after completing the recommended course of CsA, the patient developed floaters after discontinuation of the therapy in September, 1994.

The visual acuity was 20/20 in both eyes. The anterior segments were within normal limits. Vitreous showed 1É2+cells in both eyes.

Fundus Photos and FA shows the following:



Fundus OD \*\*\*\*\* FA OD



Fundus OS \*\*\*\*\* FA OS

Remarkable staining of the vessels was noted peripherally in both eyes.

Based on her symptoms and fluorescein studies, we thought she had reactivation of her Birdshot and was advised to resume CsA therapy in full dosages.

As of July, 1996, the patient has been completely symptom free with a visual acuity of 20/20 in both eyes. Cyclosporin was discontinued in March, 1996.

#### INTRODUCTION

Birdshot retinochoroidopathy is a chronic inflammatory disease affecting the posterior segment of the eye. Active birdshot retinochoroidopathy leads to severe visual impairment within first few years of follow-up, if no treatment is administered (Ocular Infections & Immunity, Mosby-Yearbook, Inc. 1996 pp. 570-78).

The disease was described by Ryan and Maumenee in 1980, named because the fundus develops multiple, small white spots that has a pattern seen with birdshot in the scatter from a shotgun.

## EPIDEMIOLOGY

BSRC is a rare disease which affects middle age, otherwise healthy individuals. It is more common in women and Caucasians of Northern European extraction than any other ethnic or racial groups.

## CLINICAL PRESENTATION

### Ocular Findings

The patient usually complains of floaters and blurring of vision in one or both eyes. They may also complain of disturbances in color vision and difficulty with dark adaptation. Typically, the review of systems is negative. These patients may have 20/20 Snellen acuity and still complain of disabling visual handicap because of difficulties with dark adaptation and poor color vision.

### Systemic Findings

Some patients also give a history of depression and sleep cycle disruption, out of proportion to their visual symptoms. Priem and Associates (BJO, 72 : 646-659, 1988), in a large study from Europe, reported a higher incidence of vascular diseases and open angle glaucoma in a cohort of patients with BSRC.

## PHYSICAL EXAMINATION

### External Examination

The globe is white and quiet in most cases. Some patient may have mild non-granulomatous anterior uveitis with fine KPs. It is unusual to have synechiae and posterior subcapsular cataract even in long standing cases. Slit lamp biomicroscopy of vitreous shows variable degrees of inflammation.

### Fundus Findings

The most striking feature in all patients is the cream colored spots in the fundus. However the pathogenesis of these fundus lesions is not clear. According to Ryan and Maumenee, These may be related to previous accumulation of fluid, more likely beneath the sensory retina than beneath RPE or to inflammatory foci in the choroid or the RPE.

Gass postulates that they are caused by focal depigmentation of the choroidal melanocytes and believe them to be analogues to vitiligo of skin. However the association between Birdshot and Vitiligo is not well established.

In addition to the distinctive lesion some patients may have optic disc edema and cystoid macular edema

## ETIOPATHOGENESIS

Retinal autoimmunity seems to play a role in the pathogenesis of this disease, particularly in the perpetuation of intraocular inflammation. The pineal gland and the retina have a common embryologic origin. They share common antigens and can both be involved in the autoimmune inflammatory reactions, and in fact this is the case in experimental models. This might be the explanation for the dysphoria observed in some patients; however this is speculative at this time.

The association between BSRC and HLA-A29 is well established. This is the strongest HLA and disease associations, and particularly the strongest between any disease and HLA-A locus with relative risk of 224. Birdshot patients belong to the HLA-A29 subtype 2 while subtype 1 seems to be protective against the disease. It is interesting that BSRC had never been observed among people from South East Asia, where HLA-A29 antigen is seldom found.

The antigenic peptides such as retinal S-Ag are produced within cytoplasm, transported by peptide transporters to the endoplasmic reticulum. Here both HLA and antigenic peptides are put together and then transported to the cell surface, where they are recognized by sensitized CD8+Tcells.

If we can decipher the sequence of amino-acid in the peptide binding cleft of the HLA moiety, we may be able to clone CD8+Tcells responding to the peptide -MHC complex and find new ways of treatment.

In a study from France (Proc. Natl. Acad. Sci. April, 1996) the authors determined the peptide binding motif of the HLA-A29 molecule. Using this motif they synthesized six peptides from Human retinal S-Ag. Two of these peptides bound efficiently to HLA-A29 molecules. The authors conclude that this study could contribute to the prediction of T-cell epitopes from retinal autoantigens implicated in Birdshot Retinopathy.

#### LABORATORY WORK-UP

Laboratory work-up are performed to exclude other conditions such the infectious causes of uveitis and the masquerade syndrome. HLA-A29 typing is helpful in confirming the diagnosis. Lymphocyte proliferation assay to retinal S-antigen and IRBP can further support the diagnosis.

#### Electrophysiology

1. ERG shows reduced amplitude and increased latency of the "b" wave or sometimes absence of Oscillatory potentials. The "a" wave is well preserved in most cases.
2. Dark adaptation shows a markedly reduced Rod and often Cone function.
3. EOG shows marked reduction of the slow wave Oscillations with preservation of fast wave oscillations

Currently we strongly feel that sequential ERG testing has a bigger role to play in the management of patients with Birdshot than previously thought. We have initiated a study to further explore this hypothesis.

#### Fluorescein Angiography

FA demonstrates the breakdown of inner blood retinal barrier, resulting in the profuse leakage of dye from the retinal vessels and capillaries. The Birdshot lesions so distinctive on ophthalmoscopy are rather unimpressive on FA. Some of these spots reveal hypofluorescence in the early phase with slight hyperfluorescence in the late phase, however many of them can remain silent during all phases of angiography.

#### Indocyanine Green Angiography ( ICG)

ICG can detect unsuspected lesions and also gives a better idea of the severity of choriocapillary and choroidal involvement in this disease.

#### NATURAL HISTORY

BSRC is a chronic disease with exacerbations and remissions, with progressive decrease in

vision within the first few years of follow up, if no treatment is administered (reference).

## HISTOPATHOLOGY

The histopathology of an eye from a patient with Birdshot showed granulomatous inflammation in and under the retina ; The same patient also had in vitro proliferative response of lymphocyte to retinal S-Ag.

The choroid shows mild granulomatous inflammation which is thought to be secondary in nature. These pathological features are similar to those observed in retinal S-Ag induced experimental autoimmune uveitis in monkeys and other animal models.

### \*\*DIFFERENTIAL DIAGNOSIS

\*The differential diagnosis includes:-

- \*1. Pars planitis
- \*2. AMPPPE
- \*3. MEWDS
- \*4. Intraocular lymphoma
- \*5. Multifocal choroiditis
- \*6. Ocular infections with choroidal involvement:
  - Syphilis
  - Lyme disease
  - Tuberculosis
  - Pneumocystis carinii
  - Sarcoidosis
- \*7. Non - infectious uveitides with choroidal involvement:
  - Sympathetic ophthalmia
  - VKH syndrome

### TREATMENT

- \*1. Steroids:
  - Systemic
  - Sub-tenon
  - Topical
- \*2. Cyclosporin-A
- \*3. Oral tolerization of retinal S-antigen

Periocular and systemic steroids have not shown consistent efficacy. High doses of prednisone can initially produce improvement in vision but patients can become rapidly dependent on it. Periocular steroids are of temporary benefit for patients with CME or severe inflammation or in flare-ups. Topical steroids are of no help in this disease.

A study by Vitale & Foster (Ophthalmology 1994; 101: 822-831) clearly demonstrated the safety and efficacy of low dose Cyclosporin-A in the management of patients with birdshot. This study also showed that a favorable visual outcome could be obtained without any demonstrable Cyclosporin-A associated nephrotoxicity and secondary side effects.

Our guidelines for therapy are as follows:

1. The presence of intraocular inflammation rather than visual acuity is considered as the primary indicator for the initiation of therapy with Cyclosporin-A.
2. Some use visual acuity rather than presence or absence of floaters as the gauge of treatment.

Since the mechanism of visual loss is inner retinal involvement, rather than choroidal involvement, the treatment is directed towards the retinal component.

3. Low dose Cyclosporin-A (2.5-5 mg/kg/day) alone or with azathioprine (1.5-2 mg/kg/day) is recommended for at least a year; then Cyclosporin-A is tapered slowly, provided complete control of inflammation has been achieved.

4. Sub-tenon's steroids are used to reduce vitreal inflammation and CME.

Oral Tolerization with Retinal S-Antigen:

The aim of tolerization with retinal S-antigen is to stimulate the body's own suppressive mechanism to overcome the inflammatory response in the eye. This form of therapy is deemed to be more specific and effective and non-toxic. This has been proved to be effective in experimental autoimmune uveitis models, and a randomized, masked, placebo controlled clinical trial has been completed by the National Eye Institute (NEI) in collaboration with the Immunology Service of the Massachusetts Eye and Ear Infirmary. The results of this study have been submitted for publication. The experiment showed that for some patients with posterior uveitis (including patients with BSRC), who respond in vitro to retinal S- antigen, feeding of retinal S- antigen enables the patient to reduce (and some cases even stop) the systemic immunosuppressive chemotherapy previously needed to stop the blinding consequences of the disease. Additional studies along these lines are being planned by the NEI.

### **Questions for Birdshot Retinochoroidopathy**

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1. Birdshot Retinochoroidopathy (BSRC) is most frequently seen in :

- a) African Americans
- b) South East Asians
- c) Caucasians of North Europe
- d) Hispanics

2. BSRC frequently affects :

- a) Children
- b) Adult male
- c) Middle aged women
- d) Elderly people

3. BSRC primarily affects :

- a) Anterior segment
- b) Posterior segment
- c) Both anterior & posterior segment
- d) Pars plana

4. All are true regarding BSRC EXCEPT:

- a) This disease was first described by Ryan & Maumenee
- b) The patient may have 20/20 Snellen acuity and still complain of visual handicap
- c) The anterior segment shows mutton fat KPs'
- d) It is unusual to have synechiae and posterior subcapsular cataract even in long standing cases

5. The most characteristic clinical finding in BSRC is :
- Vitritis
  - Snowball opacities in vitreous
  - Multiple white or cream colored spots deep in the retina or in the choroid
  - Granulomatous inflammation with mutton fat KP
6. BSRC "predisposition" is linked to HLA genotype:
- B51
  - B27
  - A29
  - DR2
7. ERG findings in BSRC include :
- Reduced amplitude and increased latency of the "b" wave
  - Well preserved "a" wave in most cases
  - Reduced Rod and often Cone function
  - All of the above
8. All are true about fluorescein angiography in BSRC EXCEPT :
- There is breakdown of inner blood retinal barrier
  - Perivascular fluorescence is noted in active disease
  - Active Birdshot lesions show early hypo and late hyperfluorescence
  - The breakdown of outer blood retinal barrier is typical
9. The treatment of choice for BSRC is :
- Topical steroids
  - Systemic steroids
  - Cyclosporin A
  - Oral tolerization of retinal S- antigen
10. Following are TRUE for Etiopathogenesis of BSRC EXCEPT :
- Autoimmunity to retinal-S antigen may play an important role
  - The pineal gland may also be involved in the inflammatory process
  - BSRC is probably caused by an RNA virus
  - The HLA-A29 subtype one appears to be protective against this disease.

Answers to Birdshot Retinochoroidopathy Review Questions

- C
- C
- B
- C
- C
- C
- D
- D
- C



10. C