HLA-A29-Positive Uveitis: Birdshot Chorioretinopathy, What Else?

Ilaria Zucchiatti Elisabetta Miserocchi Riccardo Sacconi
Francesco Bandello Giulio Modorati

Department of Ophthalmology, University Vita-Salute, Scientific Institute San Raffaele,
Milan, Italy

Key Words

Birdshot chorioretinopathy · Epidemiology · HLA-A29 · Uveitis

Abstract

Birdshot chorioretinopathy (BSCR) is a relatively rare form of uveitis, which is strongly correlated with the histocompatibility leukocyte antigen (HLA)-A29 class I type. Nevertheless, HLA typing is not diagnostic. The purpose of the present study was to retrospectively evaluate the ocular manifestations associated with the presence of HLA-A29 other than typical BSCR. Charts of consecutive patients with a diagnosis of intraocular inflammation and who were found to be positive for the presence of HLA-A29 were retrospectively reviewed. Only 7 patients met the criteria for a definite diagnosis of BSCR. Among the other 11 patients, the disease was bilateral in 7 patients and unilateral in 4 patients. A definite diagnosis of the following conditions were found: intraocular and CNS lymphoma in 1 patient, posterior tubercular uveitis with occlusive vasculitis in 1 patient, latent ocular tuberculosis in 1 patient, Fuchs' uveitis in 1 patient, herpetic panuveitis in 1 patient and HLA-B27 anterior uveitis in another patient. Although BSCR is strongly related to the HLA-A29 phenotype, and its presence confers a relative risk of disease, the definite diagnosis requires specific ocular characteristics. HLA-A29 typing alone is not a diagnostic requirement for the definite diagnosis of BSCR and should only be considered as a supportive finding.

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Introduction

Birdshot chorioretinopathy (BSCR) is a relatively rare form of uveitis, occurring in approximately 8% of posterior uveitis in the United States [1–6]. It is correlated with the

Ilaria Zucchiatti, MD
Department of Ophthalmology
University Vita-Salute, Scientific Institute San Raffaele
Via Olgettina 60, IT–20132 Milan (Italy)
E-Mail ilaria.zucchiatti@gmail.com

histocompatibility leukocyte antigen (HLA)-A29 class I type [7], even though this is not required for the diagnosis. It has been reported that 85–95% of BSCR patients express HLA-A29, whereas the prevalence of HLA-A29 is only 7% in the general population [1, 8–10]. The positive predictive value of HLA-A29 has been evaluated to be less than 50% [11]. The results of the International Consensus Conference [12] highlighted that HLA-A29 is only a supportive finding for diagnosis, and, thus, it is not a required criteria.

Even if HLA-A29 typing may be useful clinically in the identification of BSCR, physicians should be aware that in some cases HLA-A29-positive uveitis could be something other than typical BSCR. The aim of the present study is to retrospectively review the ocular manifestations associated with the presence of HLA-A29.

Design and Methods

All consecutive patients with uveitis who were found to be positive for HLA-A29 and seen at the Ocular Immunology and Uveitis Service of the Scientific Institute San Raffaele, Milan, Italy, between May 2006 and January 2011 were retrospectively reviewed. Data were obtained by reviewing the patients' charts, from a database and, in selected cases, using fluorescein angiograms and optical coherence tomography scans. At baseline and follow-up visits, all patients underwent a complete ophthalmologic evaluation, including best-corrected visual acuity, tonometry, slit-lamp examination and fundus biomicroscopy, with assessment of the grade of inflammation in the anterior chamber and vitreous according to the SUN classification [13]. Fluorescein angiography and optical coherence tomography evaluations were performed if required. Laboratory tests for infection (including syphilis, toxoplasmosis, tuberculosis and herpetic infections) and autoimmune diseases (including sarcoidosis, Behçet's disease and Vogt-Koyanagi-Harada syndrome) were performed at baseline on all patients. Systemic and topical therapies were reported at each visit.

All patients were analyzed using the Levinson criteria for the diagnosis of BSCR [12]. The required characteristics were bilateral disease, the presence of at least 3 peripapillary 'birdshot lesions' inferior or nasal to the optic disk in 1 eye, a low-grade anterior segment intraocular inflammation (defined as $\leq 1+$ cells) and finally a low-grade vitreous inflammation (defined as $\leq 2+$ vitreous haze). Birdshot lesions were defined as cream-colored, irregular or elongated, choroidal lesions with indistinct borders, the long axis of which is radial to the optic disk [12]. The ocular inflammatory activity was assessed according to the Standardization of Uveitis Nomenclature Working Group. Supportive findings for the diagnosis of BSCR were as follows: HLA-A29 positivity, retinal vasculitis and cystoid macular edema (CMO). Exclusion criteria for the diagnosis of BSCR were the presence of keratic precipitates, posterior synechiae and the presence of infectious, neoplastic or other inflammatory diseases that can cause multifocal choroidal lesions, as reported by Levinson et al. [12].

Demographic data of the pooled patients, including age, sex, and duration of follow-up were recorded. Main outcome measures included the percentage of BSCR and non-BSCR cases in the pooled HLA-A29-positive uveitis cases, based on the referred guidelines for BSCR. In case of non-BSCR uveitis, final definite ocular diagnosis was reported, based on all the findings of the intraocular inflammation. The cases of masquerade syndrome were also analyzed.

Findings

A total of 18 patients with a diagnosis of intraocular inflammation who were found to be positive for the presence of the HLA-A29 were included in the analysis (table 1). There were 32 affected eyes; the disease was bilateral in 14 patients. Five patients were male and 13 were female, the mean age was 48 ± 16 years (range 19–80 years) and mean follow-up was 25.7 ± 21.3 months (range 2–60 months).

Only 7 (38.9%) patients met the criteria for a definite diagnosis of BSCR and HLA-A29 positivity (table 2, fig. 1). Six were female and only 1 was male; the mean age at onset of ocular inflammation in this group was 54 years. Five out of 7 patients had retinal vasculitis, and 4 out of 7 had CMO as supportive findings. Furthermore, 2 out of these 7 patients had papillitis, 2 had inflammation in peripheral retina, 2 had choroidal neovascularization and 1 had branch retinal vein occlusion.

In the other 11 (61.1%) patients (7 female and 4 male), the mean age at onset of intraocular inflammation was 44 ± 19 years, with a range from 19 to 80 years (table 3). The disease was bilateral in 7 and unilateral in 4 patients. Birdshot lesions were found in 3 out of 12 patients, a mild anterior ocular inflammation ($\leq 1+$ cells) was detected in all patients and a low-grade vitreous inflammation ($\leq 2+$ vitreous haze) was present in 10 out of 11 patients.

Anterior and posterior segment ocular manifestations encountered are listed in table 3.

One patient was initially diagnosed with BSCR, but during follow-up the lack of response to immunosuppressive treatment required a further work-up assessment. The patient underwent a brain MRI and lumbar puncture showing a definite diagnosis of intraocular and CNS lymphoma (masquerade syndrome, fig. 2). One patient had a positive PPD skin test and a definite diagnosis of posterior tubercular uveitis with occlusive vasculitis; the following diagnoses were also made: latent ocular tuberculosis in 1 patient, Fuchs' uveitis in 1 patient, herpetic panuveitis (PCR-analysis positive for HSV-DNA on aqueous humor) in 1 patient and HLA-B27 anterior uveitis in another patient.

Conclusion

BSCR is an autoimmune condition, but its pathogenesis remains unknown. BSCR is strongly associated with HLA-A29, and at least 96% of BSCR patients are HLA-A29 carriers [14]. The prevalence of HLA-A29 is about 7% in the general population [1, 8–10], while in the normal Italian population a frequency of 4.76% has been reported [15]. Although HLA-A29 seems to play a major role, the prevalence of the disease in the HLA-A29-positive population remains low, indicating that there are additional susceptibility factors for disease development.

In everyday clinical practice, we usually ask for the total HLA typing for all uveitic patients. Nevertheless, HLA typing alone should not be considered as a diagnostic tool for definite diagnosis of BSCR. In fact, even if BSCR is strongly related to the HLA-A29 phenotype, and its presence confers a relative risk of disease, the definite diagnosis requires other specific ocular characteristics.

In the present study, in fact, less than 40% of patients with HLA-A29 met the criteria for a definite diagnosis of BSCR. The other 61.1% of patients expressed different ocular findings and consequently had a different diagnosis. The subgroup with a BSCR diagnosis was for the most part female, with a mean age of 54 ± 7.3 years. Our data are consistent with those from earlier studies with a wider population, describing a female predominance and a mean reported age of 53.0 years [16].

The interest of the current study is to estimate the frequency of BSCR in the whole HLA-A29-positive uveitis population. The results of our small study indicate that almost one third of patients with ocular inflammation actually have BSCR. To our knowledge, this is the first study that analyzes the percentage of non-BSCR HLA-A29-positive uveitis patients in clinical practice and evaluates the ocular manifestations of the other clinical entities. In 6 out of 11 patients, a specific etiological classification was established: intraocular and CNS lymphoma, lupus, latent ocular tuberculosis and HLA-B27 anterior uveitis.

Diagnosis of BSCR is most challenging at the onset of the disease, particularly if the typical birdshot lesions are subtle. In this study, 1 patient with an initial diagnosis of BSCR was found to be affected instead by CNS lymphoma. In clinical practice, different confounding features of ocular inflammation may be present and this should prompt the ophthalmologist to include other important differential diagnoses. The differential diagnosis of uveitis is extensive and undergoes change with time. In the present work, no definite etiological diagnosis could be determined in 5 out of 18 patients.

Our study has several limitations: it is short term, retrospective and evaluates a small study population. However, HLA-A29-positive uveitis is a relatively uncommon disease, and therefore it will take a long time to recruit a larger sample. Nevertheless, these results are valuable and reflect the demographic and causative pattern of uveitis in the pooled HLA-A29-positive patients.

In conclusion, our findings demonstrated that 61.1% of HLA-A29-positive uveitis could be something other than BSCR. Frequently, in clinical practice, HLA-A29 positivity leads ophthalmologists to erroneously formulate the diagnosis of BSCR, while they should consider other different entities of ocular inflammation. HLA-A29 typing alone is not a diagnostic requirement for the definite diagnosis of BSCR and should only be considered as a supportive finding.

Disclosure Statement

None of the authors has a conflict of interest and no financial support was received for this work.

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Partial results of this study were presented at the ARVO Annual Meeting in 2008.

Table 1. Evaluation of the ocular manifestations of all the HLA-A29-positive uveitis cases, using the Levinson criteria for the diagnosis of BSCR (1 = present, 0 = absent)

Case	Age, years	Sex	Bilateral	Dots	≤1+ AC cells	≤2+ vitreous haze	HLA-A29	Retinal vasculitis	CMO	Keratic precipitates	Posterior synechiae	Infectious disease	Neoplastic disease	Inflammatory disease
1	60	F	1	1	1	1	1	1	0	0	0	0	0	0
2	62	F	1	1	1	1	1	1	1	1	0	0	0	0
3	41	F	1	1	1	1	1	0	0	0	0	0	0	0
4	58	F	1	1	1	1	1	1	1	0	1	0	0	0
5	54	M	1	1	1	1	1	1	0	0	0	0	0	0
6	54	F	1	1	1	1	1	0	1	0	0	0	0	0
7	48	F	1	1	1	1	1	1	1	0	0	0	0	0
8	22	M	1	0	1	1	1	1	1	0	0	0	0	0
9	42	F	1	1	1	1	1	1	1	0	1	1	0	0
10	80	F	0	0	1	1	1	0	0	0	0	0	0	1
11	42	M	1	1	1	1	1	1	0	0	0	1	0	0
12	45	F	1	1	1	0	1	1	1	0	0	0	1	0
13	50	M	1	0	1	1	1	0	0	0	1	0	0	0
14	19	F	0	0	1	1	1	0	0	1	0	0	0	1
15	27	M	1	0	1	1	1	1	1	0	0	0	0	0
16	72	F	0	0	1	0	1	0	0	1	0	0	0	0
17	43	F	1	0	1	1	1	0	0	0	0	0	0	0
18	42	F	0	0	1	1	1	0	1	1	0	0	0	0

Table 2. Final diagnosis of all the patients

Case	Follow-up, Diagnosis months	Complications
1	60	birdshot
2	43	birdshot
3	26	birdshot
		choroidal neovascularization
4	39	birdshot
5	56	birdshot
6	19	birdshot
		choroidal neovascularization
7	10	birdshot
8	44	idiopathic retinal vasculitis
9	60	tuberculous optic neuropathy
10	12	scleritis
11	32	tuberculous vasculitis
12	5	CNS lymphoma
13	3	non-granulomatous with synechiae
14	39	Fuchs' uveitis
15	7	inflammation in peripheral retina
16	3	granulomatous panuveitis
17	2	bilateral anterior uveitis HLA-B27
18	2	herpes simplex virus panuveitis

Table 3. Clinical features and diagnosis of non-birdshot uveitis

Pa-tient	Age, years	Sex	Mono/bilateral	Dots	Retinal vasculitis	CMO	Keratic precipitates	Posterior synechiae	Inflammation in peripheral retina	Papillitis	Diagnosis
8	22	M	bilateral	no	yes	yes	no	no	yes	yes	idiopathic retinal vasculitis
9	42	F	bilateral	yes	yes	yes	no	yes	no	no	tuberculous optic neuropathy
10	80	F	mono	no	no	no	no	no	no	no	scleritis
11	42	M	bilateral	yes	yes	no	no	no	yes	no	tuberculous vasculitis
12	45	F	bilateral	yes	yes	yes	no	no	yes	no	CNS lymphoma
13	50	M	bilateral	no	no	no	no	yes	no	no	non-granulomatous with synechiae
14	19	F	mono	no	no	no	yes	no	yes	no	Fuchs' uveitis
15	27	M	bilateral	no	yes	yes	no	no	yes	no	inflammation in peripheral retina
16	72	F	mono	no	no	no	yes	no	no	no	granulomatous panuveitis
17	43	F	bilateral	no	no	no	no	no	no	no	anterior uveitis HLA-B27
18	42	F	mono	no	no	yes	yes	no	no	no	herpes simplex virus panuveitis

Fig. 1. Fluorescein angiography of right (a) and left (b) eyes of a typical case of BSCR.

Fig. 2. Black and white fundus photography of right (a) and left (b) eyes showing the left eye of the patient with CNS lymphoma.