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The immunopathogenesis of birdshot chorioretinopathy; a bird of many feathers

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ABSTRACT

Birdshot chorioretinopathy (BSCR) is a bilateral chronic intraocular inflammation or posterior uveitis that preferentially affects middle-aged Caucasians. BSCR is characterized by distinctive multiple choroidal hypopigmented lesions in combination with retinal vasculitis and vitritis, and the extraordinary feature that virtually all patients are HLA-A29 positive. Its pathophysiology is still poorly understood. BSCR is the strongest documented association between HLA and disease in humans, which makes it an excellent model for studying the underlying immuno-genetic mechanisms of HLA class I-associated diseases. Although the association with HLA-A29 suggests that it is directly involved in the presentation of peptide antigens to T cells, the exact contribution of HLA-A29 to the pathophysiology of BSCR remains enigmatic. This article revisits the HLA-A29 peptidome using insights from recent studies and discusses why HLA-A29 can be considered a canonical antigen presenting molecule. The first genome-wide association study facilitated novel concepts into a disease mechanism beyond HLA-A29 that includes strong genetic predisposition for the *ERAP2* gene that affects antigen processing for HLA class I. Furthermore, patients manifest with pro-inflammatory cytokine profiles and pathogenic T cell subsets that are associated with IL-17-linked inflammation. We are beginning to understand that the underlying biology of BSCR comprises various pathologic aspects branched into multiple molecular pathways. We propose to employ *Systems Medicine* to reveal their dynamic interplay for a holistic view of the immunopathology of this intriguing archetypal HLA class I-associated disease.

Contents

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1. Introduction

Birdshot chorioretinopathy (BSCR) is an organ-specific, presumably auto-immune disorder of the eye typically affecting middle aged and elderly individuals of European descent (Shah et al., 2005). BSCR manifests as a severe progressive intraocular inflammation of the posterior eye segment, typically leading to extensive retinal atrophy resulting in visual field loss, and is potentially blinding. Patients frequently complain of blurred vision especially in low light conditions, difficulties in distinguishing colors, floaters and poor contrast sensitivity and present with various symptoms including fluctuating vision, glare, decreased peripheral vision, metamorphopsia, and decreased depth perception (Shah et al., 2005). The most characteristic disease hallmarks are the numerous distinct white-creamy light spots scattered throughout the fundus that appear like birdshot from a shotgun (Fig. 1) (Howe et al., 1997; Kiss et al., 2006; Shah et al., 2005). Hence, the term *birdshot chorioretinopathy* was introduced by Ryan and Maumenee in 1981 (Ryan and Maumenee, 1980).

BSCR is clinically well-distinguishable from other posterior uveitis entities, but its underlying cause is still unknown. Evidence for any distinctive mode of inheritance is lacking, however, BSCR has been observed in monozygotic twins and has been reported in members of the same family (Fich and Rosenberg, 1992; Trinh et al., 2009). It was hypothesized that BSCR may be associated with infectious agents, including *Borrelia burgdorferi* or *Coxiella burnetii* (Kuhne et al., 1992; Suttorp-Schulten et al., 1993). Scarce extra-ocular manifestations including hearing loss, cutaneous vitiligo, psoriasis and presence of systemic sarcoidosis have only incidentally been reported (Gass, 1981; Heaton and Mills, 1993; Hesse et al., 1993; Yoshioka et al., 1983). Systemic hypertension, frequently seen in middle-aged Caucasians, is the most commonly reported non-ocular event in BSCR (Gasch et al., 1999; Priem, 1989; Rothova et al., 2004). However, no systemic disease or specific extra-ocular manifestations have been convincingly associated with BSCR (Gasch et al., 1999; Pagnoux et al., 2010).

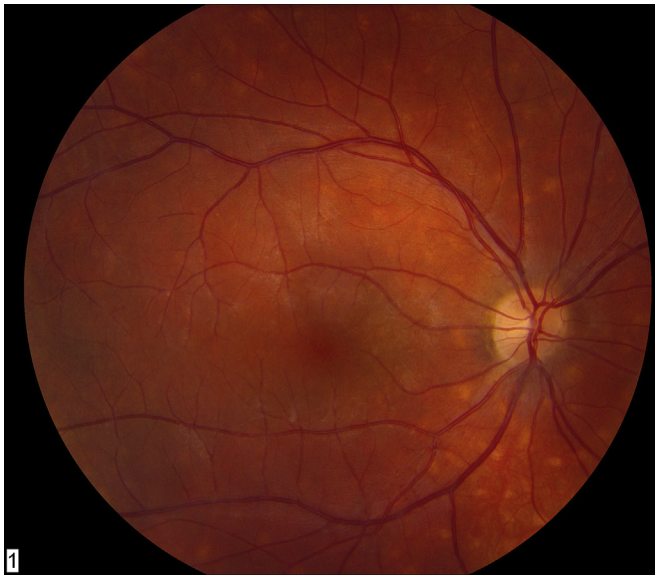

Fig. 1. Fundus photography of a patient with birdshot chorioretinopathy showing hallmark creamy yellow-orange chorioretinal lesions along the main retinal vessels.

The aim of this review is to provide an update on recent novel insights and emerging concepts of immuno-genetics that underlie the pathophysiology of BSCR.

2. The role of HLA-A29

A unique feature to BSCR is the extraordinary link with the human leukocyte antigen (HLA)-A29. Essentially all patients carry a particular variant of the HLA-A29 allele which represents one of the strongest associations between an HLA class I allele and human disease (Nussenblatt et al., 1982; Priem et al., 1988). Although the link with HLA-A29 has been well-known for over three decades, the association is both intriguing and puzzling, since its role in the pathophysiology of BSCR is not conclusive (Nussenblatt et al., 1982). Consequently, HLA-A29, present in about 7–10% of Caucasian population, is currently not essential for diagnosis (Levinson et al., 2006). Curiously, HLA-A29 has also been associated with non-classical forms of iron overload and incidentally to chromoblastomycosis (Porto et al., 1998; Tsuneto et al., 1989). The HLA-A29 serotype can be subdivided in at least 17 distinct subtypes (Holdsworth et al., 2009), but the predominant subtypes in Caucasians and patients are HLA-A*29:02 and HLA-A*29:01. Accordingly, these two subtypes have both been associated with BSCR (Lehoang et al., 1992; Levinson et al., 2004). The much rarer allele HLA-A29*10 has only been incidentally reported in patients (Donvito et al., 2010). The very similar HLA-A*29:02 and HLA-A*29:01 have only a minor amino acid difference which does not seem to affect interaction with the presented peptides. In fact, the amino acid sequence of HLA-A29 in BSCR patients is not different from unaffected HLA-A29-positive individuals (Donvito et al., 2005). Since HLA-A29 itself did not seem to bear pathogenic alternations, it was hypothesized that the HLA-A29 association merely represented a bystander marker in linkage disequilibrium with pathogenic polymorphisms in the MHC region (Levinson, 2007). However, previous reports on the investigation of short tandem repeats near *HLA-A* in small patient cohorts revealed highly various haplotypes for A*29:01, A*29:02, and A*29:10, suggesting that HLA-A29 itself confers risk to developing to BSCR (Donvito et al., 2005, 2010).

In depth genetic profiling of the entire MHC region could provide an answer to questions on the role of HLA-A29 in BSCR. With this in mind, Kuiper et al. recently investigated the entire *MHC* region of 117 Dutch and Spanish patients using genotyping and subsequent high-