LETTER TO THE EDITOR

Birdshot chorioretinopathy in a male patient with facioscapulohumeral muscular dystrophy

Evangelia Papavasileiou and Ann-Marie Lobo

Abstract

Background: We report a case of birdshot chorioretinopathy (BSCR) in a patient with facioscapulohumeral muscular dystrophy (FSHD). A 40-year-old male with history of facioscapulohumeral muscular dystrophy with significant facial diplegia and lagophthalmos presents for an evaluation of bilateral choroiditis with vasculitis and optic disc edema. Clinical examination included fundus and autofluorescence photographs, fluorescein angiography, and optical coherence tomography. To our knowledge, this patient represents the first reported case of birdshot chorioretinopathy with facioscapulohumeral muscular dystrophy. Patients with FSHD can present with ocular findings and should be screened with dilated fundus examinations for retinal vascular changes and posterior uveitis.

Keywords: Birdshot chorioretinopathy; Facioscapulohumeral muscular dystrophy

Findings

A 40-year-old man with past medical history of facioscapulohumeral muscular dystrophy (FSHD) diagnosed at age 16 reports painless blurred vision in the left eye with nyctalopia. He noticed bilateral worsening of his vision over the past 1 year. Past ocular history was significant for bilateral pterygia and dry eye syndrome.

On presentation, visual acuities were 20/30 in both eyes (OU). Intraocular pressures were normal. External examination revealed significant facial diplegia and lagophthalmos. The slit-lamp examination showed bilateral nasal and temporal pterygia. Fundus examination showed 2+ cells in the anterior vitreous and 1+ vitreous haze, vascular sheathing, few scattered pinpoint hemorrhages, and multiple cream-colored circumscribed lesions, most notably nasal to the disc OU (Figure 1a,b).

Visual field testing showed diffuse losses OU. There was hypoautofluorescence with mottling surrounding the peripapillary region and extending along the arcades OU (Figure 1c,d).

Fluorescein angiography was notable for diffuse retinal perivascular and optic disc leakage (Figure 2a,b). OCT imaging revealed bilateral optic disc elevation (Figure 2e,f), but no macular edema or subretinal fluid (Figure 2c,d).

Full-field electoretinogram testing was normal for the right eye, with the exception of prolonged implicit time of the b-wave maximal response, and abnormal for the left eye, with reduced amplitudes of the isolated and maximal rod responses and a significantly prolonged 30 Hz cone flicker implicit time.

Serologic testing revealed + HLA A-29 and elevated AST with normal ANA titer, Lyme Ab, CBC, ALT, RPR, FTA-Abs, ACE, and lysozyme. Sixty milligrams of prednisone daily was initiated with a slow taper. On follow-up examination, there was improvement in the inflammation with resolution of vitritis, stable optic disc edema, vascular sheathing, and scattered hypopigmented choroidal lesions.

Systemic prednisone taper was continued and steroid-sparing therapy with mycophenolate mofetil was initiated.

Discussion

FSHD is a rare, familial, autosomal dominant myopathy (with a high percentage of sporadic cases) affecting 1 in 20,000 individuals and is characterized by progressive muscle weakness with focal involvement of the facial, shoulder, and upper arm muscles. There is a spectrum of severity in FSHD that appears to be under the influence of several factors. Females are less affected, as are earlier generations of affected family members [1]. Our patient had genetic testing performed which revealed an FSHD deletion mutation of allele 1 (allele size of 25 kb). A larger deletion results in an earlier and more severe disease onset.

* Correspondence: Ann-Marie_Lobo@meei.harvard.edu
1Department of Ophthalmology, Harvard Medical School, Massachusetts Eye and Ear Infirmary, Boston, MA, USA
2Ocular Immunology and Uveitis Service, Massachusetts Eye and Ear Infirmary, 243 Charles Street, Boston, MA 02114, USA

© 2015 Papavasileiou and Lobo; licensee Springer. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited.
Extramuscular manifestations of FSHD include hearing loss, retinal findings compatible with Coats disease, and mental retardation \[1,2\]. Eye involvement includes ptosis, lagophthalmos, abnormal electroretinogram findings in 70% with decreased amplitudes on flicker stimulation and cone stimulation, and a reduction of the b-wave amplitude in the scotopic electroretinogram (ERG) \[3\] and Coats-like disease \[4\]. The term retinal telangiectasia has been preferred to Coats disease because of the bilateral findings in FSHD, compared with the unilateral involvement in classic Coats disease \[1\].

Retinal vascular changes have been described in FSHD and include minor abnormalities such as telangiectasia, aneurysms, capillary nonperfusion, tortuosity of retinal vessels and microaneurysms, and severe cases of intraretinal and subretinal exudative retinopathy that mimics Coats disease in less than 2% \[1\]. Fitzsimons et al. reported a case series of 75 patients and found that peripheral retinal telangiectasia was found to be extremely common in FSHD muscular dystrophy affecting 50% to 75% of the patients. Of the 75 patients, only 4% showed posterior pole abnormalities and 1% had related visual acuity loss \[1\]. Massive exudative retinal detachment is a severe but rare manifestation of retinal capillary leakage and telangiectasia \[1,5\]. There have been reports that patients with bilateral Coats-like disease changes may have an underlying systemic or hereditary disease process, such as FSHD, incontinentia pigmenti, CRB1-associated retinal dystrophy, or familial exudative vitreoretinopathy \[6\]. Bilateral Coats disease associated with severe FSHD has been reported in an infant \[6\], three children \[5\], and an adult female \[7\]. Most patients have asymptomatic retinal telangiectasia found at ocular screening in adulthood after diagnosis of FSHD.

Birdshot chorioretinopathy (BSCR) is a relatively rare subtype of noninfectious posterior uveitis, which is strongly correlated with the human leukocyte antigen (HLA)-A29 allele even though this is not required for the diagnosis. In our case, the clinical picture was consistent with BSCR and the positive HLA-A29 confirmed our clinical diagnosis. Internationally accepted criteria for the diagnosis of BSCR are based on the presence of bilateral
mild intraocular inflammation, 'birdshot lesions,' and the absence of keratic precipitates and posterior synechiae as seen in our patient [8].

BSCR is a slowly progressive disease with profound dysfunction of vision. Blurring of vision and floaters are the most prevalent presenting complaints [9]. Macular edema occurs in up to 50% of patients with BSCR, and it is the most common cause of visual loss [10]. Our patient complained of nyctalopia and blurred vision. Vitritis and the retinal pigment epithelium (RPE) atrophy at the macula area seen in autofluorescence give a possible explanation for the impaired vision.

ERG abnormalities in patients with BSCR have been well documented. Most common findings include a reduced dim scotopic b-wave amplitude and delayed 30 Hz flicker implicit times in 70% of patients. The dim scotopic b-wave amplitude presumably relates well with night blindness and is a common finding in both BSCR and FSHD [3,11]. Our patient had full-field electroretinogram testing which was abnormal for the left eye, with a significantly prolonged 30 Hz cone flicker implicit time.

This is the first report of BSCR in a patient with muscular dystrophy. There was one reported case of a woman who was diagnosed with congenital muscular dystrophy, bilateral chorioretinitis, optic atrophy, and retinal detachment [12]. There were choroidal atrophy and RPE changes outside the macula area, in contrast with our case where RPE atrophy involved the posterior pole and the macula.

We hypothesize that there might be an underlying immunological nexus between the perivascular inflammation seen in the FSHD muscle and the retinal microvascular abnormalities that also characterize BSCR [13]. T-cells have been implicated in the pathogenesis of both diseases. Increased IL-17 levels have been demonstrated in the aqueous humor of eyes with BSCR [14], and increased serum IL-17, IL-23, and transforming growth factor-beta 1 levels have also been found to be elevated in some treatment-naïve patients with BSCR [15]. In FSHD patients, it was found that inflammatory infiltrates mainly composed by CD8 (+) T cells in muscles and perivascular infiltrates mainly constituted by CD4 (+) cells [16].
The occurrence of BSCR in a patient with FSHD raises the possibility of a common genetic etiology. BSCR is strongly associated with human leukocyte antigen HLA-A29, one of the 21 serologically defined variants of HLA-A gene [9], and FSHD is an autosomal dominant inherited myopathy that is associated in more than 95% of cases with a low number of 3.3-kb tandem repeat units, termed D4Z4, located on chromosome 4q35 [17]. In a recent genome-wide association study, ERAP2 haplotype at chromosome 5q15 was associated with BSCR, suggesting that other genes are involved in the disease process [18]. A recently described transgenic mouse model carrying the D4Z4 array of the FSHD allele developed progressive keratitis of unknown etiology resulting in blindness, supporting the possibility of extramuscular inflammation [19]. Further studies are needed to confirm any overlap of genetic loci in these two rare diseases.

BSCR is considered to be an isolated ocular disorder [20], despite a few reports in the literature describing its possible association with systemic diseases including essential hypertension, cerebrovascular accidents, hearing loss, and cutaneous immune-mediated conditions such as vitiligo and psoriasis [21]. This is the first report of BSCR with FSHD.

Patients with FSHD can present with ocular findings and should be screened with dilated fundus examination for retinal vascular changes and posterior uveitis.

Consent
Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Abbreviations
BSCR: birdshot chorioretinopathy; FSHD: facioscapulohumeral muscular dystrophy.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
EP and AMK drafted the manuscript. Both authors read and approved the final manuscript.

Authors’ information
Evangelia Papavasileiou, MD, is a retina and uveitis postdoctoral research fellow at Massachusetts Eye and Ear Infirmary.
Ann-Marie Lobo, MD, is an Assistant Professor of Ophthalmology at Harvard Medical School and the Massachusetts Eye and Ear Ocular Immunology and Uveitis Service.

Received: 9 July 2014 Accepted: 30 November 2014
Published online: 12 March 2015

References
1. Fitzsimons RB, Gurwin EB, Bird AC (1987) Retinal vascular abnormalities in facioscapulohumeral muscular dystrophy: a general association with genetic and therapeutic implications. Brain 110(pt 3):631–648
2. Pauleikhoff D, Bornfeld N, Bird AC, Messing A (1992) Severe visual loss associated with retinal telangiectasia and facioscapulohumeral muscular dystrophy. Graefes Arch Clin Exp Ophthalmol 230(4):362–365
3. Stübben JP (2007) Facioscapulohumeral muscular dystrophy: multimodal evoked potentials and electroretinogram. Electromyogr Clin Neurophysiol 47(4–5):233–241
4. Longmuir SQ, Mathews KD, Longmuir RA, Vison VL, Abrahoff MD (2010) Retinal arterial but not venous tortuosity correlates with facioscapulohumeral muscular dystrophy severity. J AAPOS 14(3):240–243
5. Shields CL, Zahler J, Fark N, Furuta M, Eagle RC Jr, Espinosa LE, Fischer PR, Shields JA (2007) Neovascular glaucoma from advanced Coats disease as the initial manifestation of facioscapulohumeral dystrophy in a 2-year-old child. Arch Ophthalmol 125(6):840–842
6. Ganesh A, Kaliki S, Shields CL (2012) Coats-like retinopathy in an infant with preclinical facioscapulohumeral dystrophy. J AAPOS 16(2):204–206
7. Vance SK, Wald JK, Sherman J, Freund KB (2011) Subclinical facioscapulohumeral muscular dystrophy masquerading as bilateral Coats disease in a woman. Arch Ophthalmol 129(6):807–809
8. Kiss A, Anzoraz F, Foster C (2000) Birdshot retinocleiochoroidopathy. Int Ophthalmol Clin 40:59–55
9. Shah KH, Levinson RD, Yu F, Goldhardt R, Gordon LK, Gonzales CR, Heckenlively JR, Kappel PJ, Holland GN (2005) Birdshot chorioretinopathy. Surv Ophthalmol 50(6):519–541
10. Papadis M, Herbert CP (2013) Reappraisal of birdshot retinochoroiditis (BRC): A global approach. Graefes Arch Clin Exp Ophthalmol 251(3):861–869
11. Comander J, Loewenstein J, Sobrin L (2011) Diagnostic testing and disease monitoring in birdshot chorioretinopathy. Semin Ophthalmol 26(4–5):329–336
12. Avoni P, Monari L, Carelli V, Carangiua R, Barbieri P, Donati C, Badiali L, Baruzzi A, Montagna P (2000) Congenital encephalopathy with epilepsy, chorioretinitis, basal ganglia involvement, and muscle minocline. Ann Neurol 47(3):395–399
13. Fitzsimons RB (1994) Facioscapulohumeral dystrophy: the role of inflammation. Lancet 344(8927):902–903
14. Kuiper JJ, Mutis T, de Jager W, de Groot-Mijnes JD, Rothova A (2011) Intraocular interleukin-17 and proinflammatory cytokines in HLA-A29-associated birdshot chorioretinopathy. Am J Ophthalmol 152(2):177–182, e1
15. Yang P, Foster CS (2013) Interleukin 21, interleukin 23, and transforming growth factor beta in HLA-A29-associated birdshot retinocleiochoroidopathy. Am J Ophthalmol 156(2):400–406, e2
16. Frisullo G, Fruscianti R, Nociti V, Tasca G, Renna R, Iorio R, Patanella AK, Iannaccone E, Marti A, Rossi M, Bianco A, Montolfre M, Tonali PA, Mirabella M, Batozzi AP, Ricci E (2011) CD8(+) T cells in facioscapulohumeral muscular dystrophy patients with inflammatory features at muscle MRI. J Clin Immunol 31(2):155–166
17. van Deutekom JC, Wijmenga C, van Tienhoven EA, Gruter AM, Hewitt JE, Padberg GW et al (1993) FSHD associated DNA rearrangements are due to deletions of integral copies of a 3.2 kb tandemly repeated unit. Hum Mol Genet 2:2037–2042
18. Kuiper JJ, Van Setter J, Rijkep S, Van T Slot R, Mulder F, Missotten T, Baarona GS, Francioli LG, Puliti SL, De Kovel CG, Ten Dam-Van Loon N, Den Hollander AI, Huis in het Veld P, Hoyningen CB, Cordero-Coma M, Martin J, Llorens V, Ayana B, Thomas D, Bakker SC, Ophoff RA, Rothova A, De Bakker PI, Mutis T, Koelman BP (2014) A genome-wide association study identifies a functional ERAP2 haplotype associated with birdshot chorioretinopathy. Hum Mol Genet 23(22):6081–6087
19. Krom YD, Thijssen PE, Young JM, den Hamer B, Balog J, Yao Z, Maves L, Snider L, Knopp P, Zammit PS, Rijker T, van Engelen BG, Padberg GW, Frants RR, Tawil R, Tapscott SJ, van der Maarel SM (2013) Intrinsic epigenetic regulation of the D4Z4 macrosatellite repeat in a transgenic mouse model for FSHD. PLoS Genet 9(4):e1003415
20. Pagnoux C, Nahr A, Acouba A, Bereze A, Monnet D, Cohen P, Levinson RD, Brezin AP, Guillemin L (2010) Extraocular manifestations of birdshot chorioretinopathy in 118 French patients. Presse Med 39(5):e97–e102
21. Prieur HA, Oosterhuis JA (1988) Birdshot chorioretinopathy: clinical charac- teristics and evolution. Br J Ophthalmol 72(9):646–659