Review Article

Inflammatory chorioretinopathies (White Dot Syndromes), diagnosis and management: A review of the literature

Bassey Fiebai, Safinatu Wada Mohammed

Department of Ophthalmology, University of Port Harcourt Teaching Hospital, Port Harcourt, Rivers State, Nigeria

Abstract

Background: The white dot syndromes or inflammatory chorioretinopathies are a heterogenous group of diseases of unknown aetiology, characterized by the appearance of white dots on the fundus. These group of disorders include, acute posterior multifocal placoid pigment epitheliopathy (APMPPE), serpiginous choroiditis, multiple evanescent white dot syndrome (MEWDS), multifocal choroiditis and panuveitis (MCP), punctate inner choroidopathy (PIC), and diffuse subretinal fibrosis (DSF). They appear to have similar modes of presentation, but subtle differences noted help in their diagnosis coupled with and imaging techniques aids in the management of these disorders.

Aim: This study aims to review relevant literature available on inflammatory chorioretinopathies, their diagnosis and management.

Methods: Review of pertinent literature and available publications using the terms 'White Dot Syndrome (WDS)', 'inflammatory chorioretinopathies' acute multifocal placoid punctate epitheliopathy, birdshot chorioretinopathy, serpiginous choroiditis, multifocal choroiditis and panuveitis and punctate inner choroiditis were sought for using a comprehensive literature search of PubMed and MEDLINE. All relevant articles, full length and abstract that had information on clinical presentations, investigations and available treatment modalities were included. Additional papers were also selected from reference lists of papers identified by the electronic database search.

Results: Reviewed information shows that the WDS though similar in presentation are still considered to be separate disease entities and not really a spectrum of the same disease as some postulate. Most are self-limiting and visual prognosis is generally good. Newer treatment modalities uncovered in this review include the use of intravitreal anti-vascular endothelial growth factors in the treatment of sight-threatening complications such as choroidal neovascularisation.

Conclusion: This article has reviewed inflammatory chorioretinopathies or WDS as reported in literature over 4 decades. An appreciable data exist and reviewed information reveals that WDS are a heterogeneous group of disorders with similar aetiology and modes of presentation but with some subtle distinct characteristics. Further studies on predictors of foveal involvement would inform what prophylactic treatments maybe beneficiary in preventing visual loss.

Keywords: Birdshot chorioretinopathy, inflammatory chorioretinopathies, White Dot Syndrome

Address for correspondence: Dr. Bassey Fiebai, Department of Ophthalmology, University of Port Harcourt Teaching Hospital, Port Harcourt, Rivers State, Nigeria.
E-mail: bassief@yahoo.com
Received: 04.11.2018, **Accepted:** 13.02.2019

Access this article online	
Quick Response Code:	Website: www.phmj.org
	DOI: 10.4103/phmj.phmj_21_18

How to cite this article: Fiebai B, Mohammed SW. Inflammatory chorioretinopathies (White Dot Syndromes), diagnosis and management: A review of the literature. Port Harcourt Med J 2019;13:1-6.

INTRODUCTION

The White Dot Syndromes (WDS) or inflammatory chorioretinopathies are a heterogeneous group of diseases of unknown aetiology.[1]

They are characterised by the appearance of white dots on the fundus.

These group of disorders include acute posterior multifocal placoid pigment epitheliopathy (APMPPE), serpiginous choroiditis (SC), multiple evanescent WDS (MEWDS), Birdshot chorioretinopathy (BSC), multifocal choroiditis and panuveitis (MCP), punctate inner choroidopathy (PIC) and diffuse subretinal fibrosis.[2,3]

Most are believed to be autoimmune in origin and are seen in individuals below the age of 50 years except in BSC and serpiginous choroidopathy.[4] Others are thought to be infectious in origin as they are associated with a viral prodrome [Figure 1].

A female preponderance is seen in BSC, MEWDS, MCP and PIC.[4]

With the exception of MEWDS, the presentation is usually bilateral and asymmetric.

An update in the literature on WDS is reviewed in this article, emphasising on the diagnosis and current trends in management.

METHODS

Available publications from 1968 to 2017 (49 years) using the terms 'WDS', 'inflammatory chorioretinopathies' acute multifocal placoid punctate epitheliopathy, birdshot choroidopathy, SC, MCP and punctate inner choroiditis were sought for using a comprehensive literature search of PubMed and MEDLINE. All relevant articles, full length and abstract that had information on clinical presentations, investigations and available treatment modalities were included. Additional papers were also selected from reference lists of papers identified by the electronic database search.

RESULTS

Reviewed information shows that the WDS though similar in presentation are still considered to be separate disease entities and not really a spectrum of the same disease as some postulate. Most are self-limiting, and visual prognosis is generally good except when there is foveal involvement. Newer treatment modalities uncovered in this review include the use of intravitreal anti-vascular endothelial growth factors (Anti-Vegfs) in the treatment of sight-threatening complications such as choroidal neovascularisation.

DISCUSSION

WDS are a rare group of idiopathic multifocal inflammatory conditions involving the choroid and retina, characterised by appearance of white dots on the fundus.[2-7] These entities have overlapping features with most presenting in an acute way but with minimal or no permanent visual impairment in the long term. Some have postulated that WDS is a clinical spectrum of the same disease entity rather than separate disease entities.

Acute posterior multifocal placoid pigment epitheliopathy

APMPEE is a rare inflammatory condition that occurs in young healthy adults.[8] Aetiology is unknown but it has been associated with human leucocyte antigen-B7 (HLA-B7) and HLA-DR2. Patients usually have a viral prodrome and the disease has also been linked to adenovirus. Other infections also reported in association with APMPEE including Lyme disease and psoriasis. A community-based population study found it to be more common in men.[3]

Its presentation is usually bilateral but asymmetric, starting in one eye first then the second one within a few days. It is still unclear if APMPEE is primarily a disease of the retina pigment epithelium (RPE) or an abnormality in the choroid/choriocapillary perfusion.

Fundus examination reveals multifocal placoid yellowish-white lesions at the level of the RPE and choroid from the posterior pole to the equator, varying in size from 1 to 2 disc areas [Figure 2].[8] Lesions resolve over 2–6 weeks leaving an area of RPE alteration of depigmentation and clumping.

Fluorescein angiography usually reveals lobular hypofluorescence in the early frames and even diffuse staining in the same areas in the late phase.

APMPPE is usually self-limiting with a generally good long-term prognosis. However, some studies have reported poor visual prognosis in older patients, likely from failure of the RPE to recover from the inflammatory insult resulting in atrophy of the RPE and overlying receptors.[3,9-11]

There is no evidence that corticosteroids or any other medications are beneficial; however, systemic steroids may

be used as well as intravitreal Anti-Vegfs, if there is foveal involvement.[11]

Serpiginous choroiditis

SC is also known as geographic helicoid peripapillary choroidopathy. It occurs in the second to seventh decade of life and has an equal sex distribution.[12-14]

The aetiology is unknown but has been associated with immune-related occlusive vasculitis and HLA B7.[15-17] It has also been linked with herpes viruses although the evidence is inconclusive.[18]

The presentation is usually unilateral and characterised by painless visual loss associated with photopsia and scotomata.[19,20] Anterior uveitis and vitritis are mild.

Fundus examination shows asymmetric bilateral lesions seen at the level of the inner choroid or RPE projecting in a geographic or polypoidal manner in the posterior pole.[2,3,12,14] Active lesions may occur in more than one area, and skipped areas are common.[21] Macular serpiginous or peripheral SC is less common.[19,21] The disease typically starts from the optic nerve and progresses in a centrifugal pattern. Visual loss is usually as a result of the development of choroidal neovascular membrane (CNVM) or macular involvement.[2,14,22]

Early frames of fundus fluorescein angiogram show blockage of the choroidal flush and staining of the active edge in the late phase.[21-23] However, early hyperfluorescence with late leakage reveals the presence of CNVM. Indocyanine green shows hyperfluorescence in all phases of the study for active and old lesions.[21,22] Fundus autofluorescence aids not only in detecting RPE damage but also in following the clinical course of the disease as areas of regressed disease activity show hypo- and hyper-autofluorescence in areas with newer active lesions.[24]

Treatment is usually with corticosteroids which could be periocular, systemic or intravitreal. However, these are not usually effective for long-term remission and immunomodulators such as azathioprine and cyclophosphamide, and other biological modulators such as cyclosporin have been used.[2,25] CNVM is treated with Anti-Vegfs or application of laser.

Multiple evanescent White Dot Syndrome

This WDS is predominantly seen in young adult females usually preceded by a viral-like illness.[4,26,27]

Presentation is with a painless monocular blurring of vision with associated photopsia and mild vitritis.[4] Lesions are usually at the level of the outer neurosensory retina and retinal pigment epithelium. Numerous small (100–300 micrometer) grey white patches sparing the fovea are seen in the posterior pole [Figure 3]. They may be replaced by mild pigment mottling. Foveal granularity is common and optic disc oedema is occasionally present.[1]

Fluorescein angiography shows early punctate hyperfluorescence in wreath-like configuration with late staining.[28] Electroretinography shows reduced a-waves and reduced early receptor potential amplitudes that would suggest a primary involvement of the outer segments of photoreceptors.[27,28] Variable visual field changes have been reported with the most common being an enlargement of the blind spot; others are temporal or paracentral scotoma.[29,30] Optical coherence tomography may show inner segment/outer segment disruption.[29,31,32]

Treatment is usually not required as the disorder is self-limiting and spontaneously resolves with good prognosis in uncomplicated cases as most eyes improve to 6/9 or better within 2–3 months.[27,31]

If complicated with a CNVM, Anti-Vegfs or laser photocoagulation can be given.

Birdshot chorioretinopathy

BSC is also known as vitiliginous choroiditis. It is a rare idiopathic autoimmune intraocular inflammatory condition, commonly seen in the fourth and fifth decades of life in females.[33-35] BSC has an unknown aetiology but associated with HLA-A29.[36,37]

The presentation is with an insidious onset of impaired central vision associated with floaters and photopsia.[34,35] There is usually mild anterior uveitis with moderate vitritis and retinal vascular leakage.[2,33] The fundus shows typical multiple hypopigmented coloured lesions at the level of the retinal pigment epithelium or deeper scattered throughout the fundus [Figure 4].[38] Other features include cystoid macular oedema and disc oedema.[33-35]

Fundus fluorescein angiogram is useful in demonstrating the presence of macular oedema and retina vascular leakage.[39]

HLA typing aids in the diagnosis.

Treatment includes the use of systemic steroids, immunosuppressants and cyclosporine.[33,34]

Multifocal choroiditis and panuveitis

This condition is an intraocular inflammation characterised by panuveitis of unknown aetiology with retinochoroidal

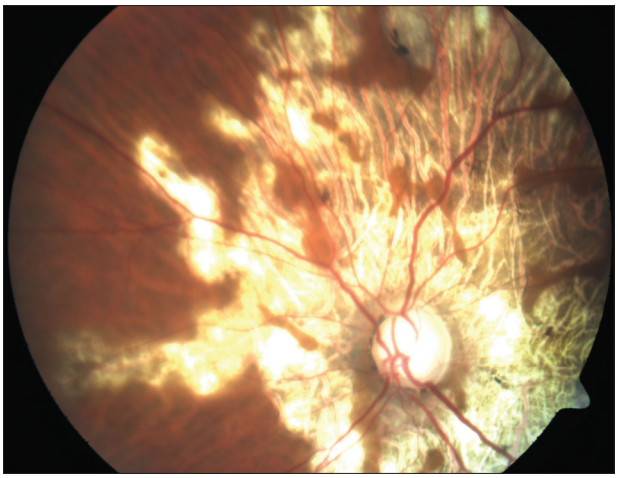

Figure 1: Serpiginous choroiditis

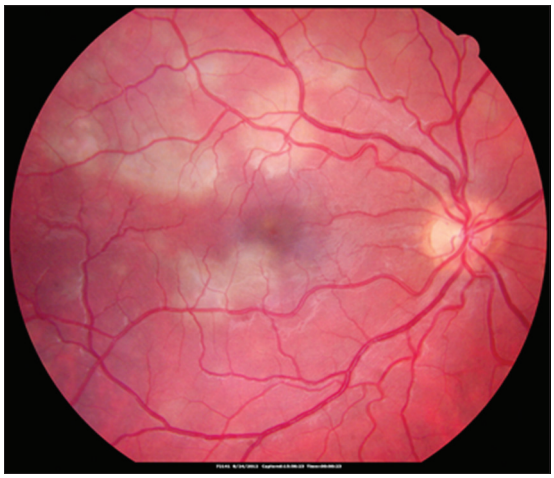

Figure 2: Acute posterior multifocal placoid pigment epitheliopathy

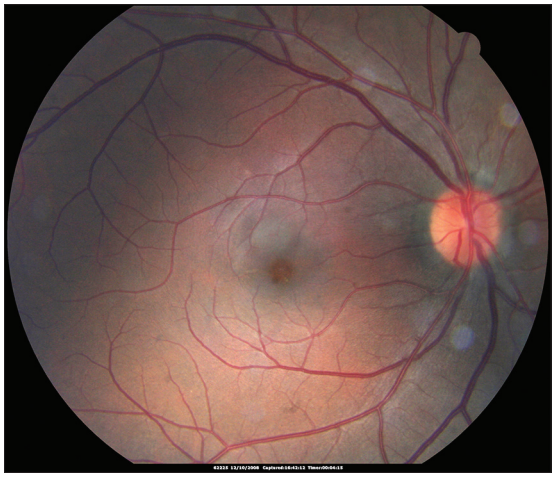

Figure 3: Multiple evanescent White Dot Syndrome

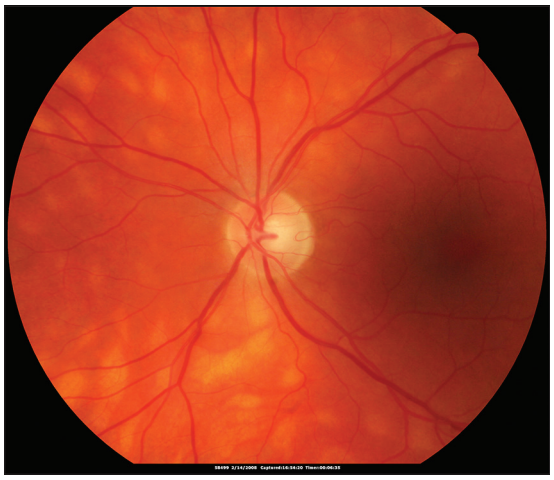

Figure 4: Birdshot chorioretinopathy

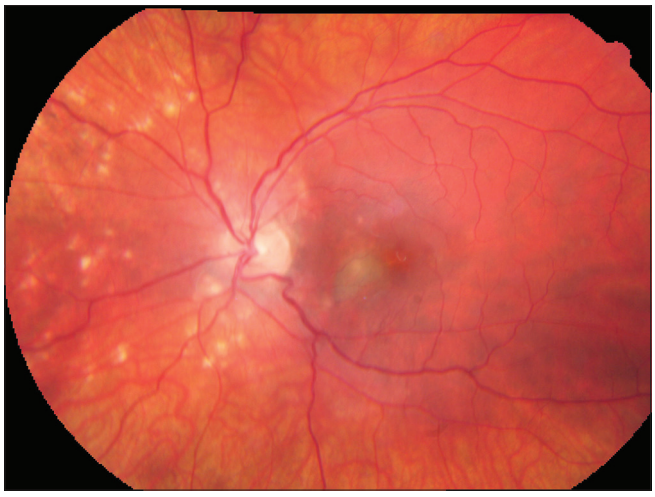

Figure 5: Multifocal choroiditis and panuveitis

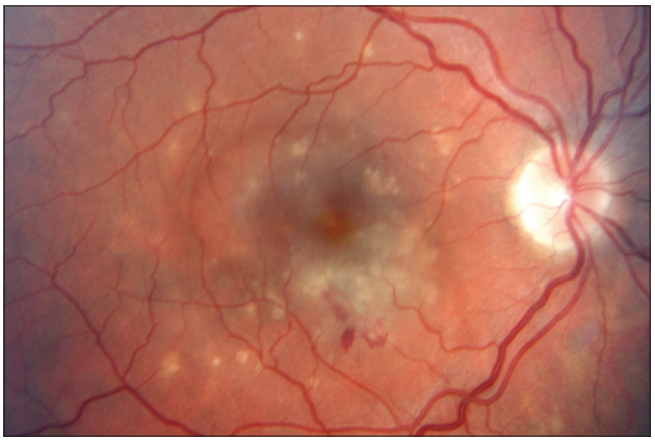

Figure 6: Punctate inner choroidopathy

lesions.[2,40] It is commonly seen between the second and sixth decades and occurs more commonly in females than males.[40,41] It is a chronic disorder with multiple recurrences.

The presentation is usually bilateral with an acute onset of blurred vision associated with floaters and photopsia.[2,40] There is usually marked anterior uveitis and vitritis. Fundus examination reveals multiple yellow or grey lesion at the level of choroid and RPE which are mainly located at the

mid periphery [Figure 5]. These active lesions may become atrophic with pigmentation with chronicity.[40,42] Linear chorioretinal streaks may be seen in the fundus.[43] There may also be swelling or hyperaemia of the optic nerve head, cystoid macular oedema, epiretinal membrane and CNVMs which are commonly responsible for the loss of vision.[2,40,44]

Visual field may reveal scotoma corresponding to areas of lesion and enlargement of blind spot.[40] Fundus fluorescein angiogram shows early hypofluorescence and late hyperfluorescence at early presentation; however, the presence of a CNVM will show early hyperfluorescence.[2]

Treatment involves the use of systemic steroids and immunosuppressive therapy (cyclosporine, azathioprine, methotrexate, chlorambucil and cyclophosphamide).[40,45]

MCP is a chronic disorder with multiple recurrences. Up to 66% of eyes achieve visual acuity of 20/40 or better.[2] Those with worse visual acuity are because of the development of CNVM or cystoid macula oedema.[2]

Punctate inner choroidopathy

PIC is a rare inflammatory ocular disease which affects mostly young women who are myopes.[46-48] Similar to MCP, however, involvement is predominantly of the posterior pole or mid periphery with no vitritis, and patients present with blurring of vision, floaters and photopsia.[48-50]

Fundus examination at the acute phase shows deep, yellow cylindrical lesions at the level of the RPE and inner choroid, measuring about 100–300 μm, and when healed, lesions become pigmented, punched out and manifest as atrophic scars [Figure 6].[46,47,50-52]

Visual field examination shows central or paracentral scotomas. Fundus fluorescein shows filling and staining at late phase.[47,53]

Treatment is with systemic steroids for lesions involving the fovea.[48,54]

Visual prognosis is good unless there is CNVM. If CNVM is present, laser photocoagulation and photodynamic therapy can be administered.[55]

CONCLUSION

This article has reviewed inflammatory chorioretinopathies or WDS as reported in literature over 4 decades. An appreciable data exist, and reviewed information reveals that WDS are a heterogeneous group of disorders with similar aetiology and modes of presentation but with some subtle distinct characteristics. Careful fundus examination backed up by multimodal imaging aids in the diagnosis. Management is based on the ability to make a good diagnosis as some are self-limiting with good prognosis such as APMPEE, MEWDS and PIC while others such as SC may develop complications which compromise vision.

Further studies on predictors of foveal involvement would inform what prophylactic treatments maybe beneficiary in preventing visual loss.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Matsumoto Y, Haen SP, Spaide RF. The white dot syndromes. Compr Ophthalmol Update 2007;8:179-200.
2. Tewari A. White Dot Syndrome. Emergency Medicine. Available from: https://www.emedicine.medscape.com/article/1227778-overview. [Last accessed on 2018 Oct 13].
3. Tibetts MD, Shah HR, Fein JG. Characterising the White Dots Syndromes. Retina Today. Available from: https://www.retinatoday.com/2016/12/characterizing-the-white-dot-syndromes. [Last accessed on 2018 Oct 13].
4. Abu-Yaghi NE, Hartono SP, Hodge DO, Pulido JS, Bakri SJ. White dot syndromes: A 20-year study of incidence, clinical features, and outcomes. Ocul Immunol Inflamm 2011;19:426-30.
5. Folk JC, Reddy CV. White dot chorioretinal inflammatory syndromes. In: Lewis H, Ryan SJ, editors. Medical and Surgical Retina: Advances, Controversies, and Management. St. Louis: Mosby-Year Book, 1994; 385-400.
6. Gass JD. Stereoscopic Atlas of Macular Diseases: Diagnosis and Treatment. 4th ed. Philadelphia: W. B. Saunders Co., 1997; 158-65.
7. Spaide RF, editor. White dot syndromes. Diseases of the Retina and Vitreous. Philadelphia: W. B. Saunders Co., 1999; 195-213.
8. Gass JD. Acute posterior multifocal placoid pigment epitheliopathy. Arch Ophthalmol 1968;80:177-85.
9. Pagliarini S, Piguet B, Ffytche TJ, Bird AC. Foveal involvement and lack of visual recovery in APMPPE associated with uncommon features. Eye (Lond) 1995;9 (Pt 1):42-7.
10. Roberts TV, Mitchell P. Acute posterior multifocal placoid pigment epitheliopathy: A long-term study. Aust N Z J Ophthalmol 1997;25:277-81.
11. Fiore T, Iaccheri B, Androudi S, Papadaki TG, Anzaar F, Brazitikos P, *et al.* Acute posterior multifocal placoid pigment epitheliopathy: Outcome and visual prognosis. Retina 2009;29:994-1001.
12. Balarabe AH. Clinical profile and outcome of serpiginous choroiditis in a uveitis clinic in India. Niger J Ophthalmol 2014;22:24-6.
13. Saurabh K, Panigrahi PK, Kumar A, Roy R, Biswas J. Profile of serpiginous choroiditis in a tertiary eye care centre in Eastern India. Indian J Ophthalmol 2013;61:649-52.
14. Abrez H, Biswas J, Sudharshan S. Clinical profile, treatment, and visual outcome of serpiginous choroiditis. Ocul Immunol Inflamm 2007;15:325-35.
15. King DG, Grizzard WS, Sever RJ, Espinoza L. Serpiginous choroidopathy associated with elevated factor VIII. Retina 1990;10:97-101.
16. Baglivo E, Boudjema S, Pieh C, Safran AB, Chizzolini C, Herbort C.

Vascular occlusion in serpiginous choroidopathy. Br J Ophthalmol 2005;89:387-8.
17. Erkkilä H, Laatikainen L, Jokinen E. Immunological studies on serpiginous choroiditis. Graefes Arch Clin Exp Ophthalmol 1982;219:131-4.
18. Priya K, Madhavan HN, Reiser BJ, Biswas J, Saptagirish R, Narayana KM. Association of herpesviruses in the aqueous humor of patients with serpiginous choroiditis: A polymerase chain reaction-based study. Ocul Immunol Inflamm 2002;10:253-61.
19. Mansour AM, Jampol LM, Packo KH, Hrisomalos NF. Macular serpiginous choroiditis. Retina 1988;8:125-31.
20. Bock CJ, Jampol LM. Serpiginous choroiditis. In: Albert DM, Jakobiec FA, editors. Principles and Practice of Ophthalmology. Vol. 1. Philadelphia: W. B. Saunders Co., 1994; 517-23.
21. Portero A, Careño E, Real LA, Villarón S, Herreras JM. Infectious nontuberculous serpiginous choroiditis. Arch Ophthalmol 2012;130:1207-8.
22. Lim WK, Buggage RR, Nussenblatt RB. Serpiginous choroiditis. Surv Ophthalmol 2005;50:231-44.
23. Gupta V, Al-Dhibi HA, Arevalo JF. Retinal imaging in uveitis. Saudi J Ophthalmol 2014;28:95-103.
24. Cardillo Piccolino F, Grosso A, Savini E. Fundus autofluorescence in serpiginous choroiditis. Graefes Arch Clin Exp Ophthalmol 2009;247:179-85.
25. Akpek EK, Jabs DA, Tessler HH, Joondeph BC, Foster CS. Successful treatment of serpiginous choroiditis with alkylating agents. Ophthalmology 2002;109:1506-13.
26. Gross NE, Yannuzzi LA, Freund KB, Spaide RF, Amato GP, Sigal R, *et al.* Multiple evanescent white dot syndrome. Arch Ophthalmol 2006;124:493-500.
27. Jampol LM, Sieving PA, Pugh D, Fishman GA, Gilbert H. Multiple evanescent white dot syndrome. I. Clinical findings. Arch Ophthalmol 1984;102:671-4.
28. Lefrançois A, Hamard H, Corbe C, Schmitt A, Badelon I, Vidal A. A case of MEWDS. "The multiple evanescent white-dot syndrome". J Fr Ophtalmol 1989;12:103-9.
29. Sheng Y, Sun W, Gu YS. Spectral-domain optical coherence tomography dynamic changes and steroid response in multiple evanescent white dot syndrome. Int J Ophthalmol 2017;10:1331-3.
30. Lim JI, Kokame GT, Douglas JP. Multiple evanescent white dot syndrome in older patients. Am J Ophthalmol 1999;127:725-8.
31. Li D, Kishi S. Restored photoreceptor outer segment damage in multiple evanescent white dot syndrome. Ophthalmology 2009;116:762-70.
32. Hangai M, Fujimoto M, Yoshimura N. Features and function of multiple evanescent white dot syndrome. Arch Ophthalmol 2009;127:1307-13.
33. Ryan SJ, Maumenee AE. Birdshot retinochoroidopathy. Am J Ophthalmol 1980;89:31-45.
34. Shah KH, Levinson RD, Yu F, Goldhardt R, Gordon LK, Gonzales CR, *et al.* Birdshot chorioretinopathy. Surv Ophthalmol 2005;50:519-41.
35. Menezo V, Taylor SR. Birdshot uveitis: Current and emerging treatment options. Clin Ophthalmol 2014;8:73-81.
36. Brézin AP, Monnet D, Cohen JH, Levinson RD. HLA-A29 and birdshot chorioretinopathy. Ocul Immunol Inflamm 2011;19:397-400.
37. Donvito B, Monnet D, Tabary T, Delair E, Vittier M, Réveil B, *et al.* Different HLA class IA region complotypes for HLA-A29.2 and -A29.1 antigens, identical in birdshot retinochoroidopathy patients or healthy individuals. Invest Ophthalmol Vis Sci 2005;46:3227-32.
38. Gass JD. Vitiliginous chorioretinitis. Arch Ophthalmol 1981;99:1778-87.
39. Guex-Crosier Y, Herbort CP. Prolonged retinal arterio-venous circulation time by fluorescein but not by indocyanine green angiography in birdshot chorioretinopathy. Ocul Immunol Inflamm 1997;5:203-6.
40. Boricean NG, Scripcă OR. Multifocal choroiditis and panuveitis-difficulties in diagnosis and treatment. Rom J Ophthalmol 2017;61:293-8.
41. Saxena S, Saxena RC. Retina Atlas a Global perspective. 1st ed. New Delhi: Jaypee Brothers Medical Publishers Pvt Ltd., 2009; 99-110.
42. Yanoff M, Duker JS. General approach to the uveitis patient and treatment strategies. In: Yanoff M, Duker JS, editors. Ophthalmology. Philadelphia: Mosby, 2009; 783-8, 21.
43. Spaide RF, Yannuzzi LA, Freund KB. Linear streaks in multifocal choroiditis and panuveitis. Retina 1991;11:229-31.
44. Thorne JE, Wittenberg S, Jabs DA, Peters GB, Reed TL, Kedhar SR, *et al.* Multifocal choroiditis with panuveitis incidence of ocular complications and of loss of visual acuity. Ophthalmology 2006;113:2310-6.
45. Goldberg NR, Lyu T, Moshier E, Godbold J, Jabs DA. Success with single-agent immunosuppression for multifocal choroidopathies. Am J Ophthalmol 2014;158:1310-7.
46. Campos J, Campos A, Mendes S, Neves A, Beselga D, Sousa JC. Punctate inner choroidopathy: A systematic review. Med Hypothesis Discov Innov Ophthalmol 2014;3:76-82.
47. Watzke RC, Packer AJ, Folk JC, Benson WE, Burgess D, Ober RR. Punctate inner choroidopathy. Am J Ophthalmol 1984;98:572-84.
48. Gerstenblith AT, Thorne JE, Sobrin L, Do DV, Shah SM, Foster CS. Punctate inner choroidopathy: A survey analysis of 77 persons. Ophthalmology 2007;114:1201-4.
49. American Academy of Ophthalmology. Retina and Vitreous. Association: Focal and diffuse choroidal and retinal inflammation. In: Basic and Clinical Science Course. Sec. 12. San Francisco, USA: American Academy of Ophthalmology, Leo, 2012; 192.
50. Campos J, Campos A, Beselga D, Mendes S, Neves A, Sousa JP. Punctate inner choroidopathy: A clinical case report. Case Rep Ophthalmol 2013;4:155-9.
51. Essex RW, Wong J, Fraser-Bell S, Sandbach J, Tufail A, Bird AC, *et al.* Punctate inner choroidopathy: Clinical features and outcomes. Arch Ophthalmol 2010;128:982-7.
52. Sá-Cardoso M, Dias-Santos A, Nogueira N, Nascimento H, Belfort-Mattos R. Punctate inner choroidopathy. Case Rep Ophthalmol Med 2015;2015:371817.
53. Knickelbein JE, Sen HN. Multimodal imaging of the white dot syndromes and related diseases. J Clin Exp Ophthalmol 2016;7. pii: 570.
54. Levy J, Shneck M, Klemperer I, Lifshitz T. Punctate inner choroidopathy: Resolution after oral steroid treatment and review of the literature. Can J Ophthalmol 2005;40:605-8.
55. Hohberger B, Rudolph M, Bergua A. Choroidal neovascularization associated with punctate inner choroidopathy: Combination of intravitreal anti-VEGF and systemic immunosuppressive therapy. Case Rep Ophthalmol 2015;6:385-9.