Annals of Medicine and Surgery 80 (2022) 104294

Contents lists available at ScienceDirect

Annals of Medicine and Surgery

journal homepage: www.elsevier.com/locate/amsu

Case Report

Tubercular Harada disease – An unreported uveitic entity

Ranju Kharel Sitaula *, Preeti Agrawal

Department of Ophthalmology, Maharajgunj Medical Campus, B. P. Koirala Lions Centre for Ophthalmic Studies, Tribhuvan University, Institute of Medicine, Kathmandu, Nepal

ARTICLE INFO

Keywords:
Granulomatous uveitis
Immunosuppression
Molecular mimicry
Tuberculosis
Vogt koyanagi harada disease
Case report

ABSTRACT

Introduction: & IMPORTANCE: Ocular tuberculosis and Vogt Koyanagi Harada disease (VKHD) both are the important cause of panuveitis. In tubercular endemic region like Nepal, latent tuberculosis (TB) may be accompanied with the features of VKHD. Hence, the aim of our publication is the use the term Tubercular Harada disease (THD) for such panuveitis with mixed features.

Case presentation: We aim to report two cases of panuveitis from Nepal with the simultaneous features of tuberculous uveitis and Harada disease managed with combined antitubercular agents and antimetabolites.

Clinical discussion: Two cases presented with bilateral decreased vision with no systemic associations. They had bilateral panuveitis and sunset glow. Ultrasonography showed the choroidal thickening, optical coherence tomography confirmed macular edema with retinal nerve fibre layer edema. Electroretinogram of both eyes showed reduced P1 wave amplitude. All the systemic investigations were normal except the positive tuberculin skin test and TB QuantiFERON Gold test.

Both of them were managed with intravenous/oral corticosteroid (1mg/kg) along with CAT- I ATT regimen (2HRZE+7HR) for 9 months and oral antimetabolites (azathioprine or methotrexate). Long term follow-up showed normal visual acuity with no evidence of recurrence of uveitis.

Conclusion: Mycobacterium could have triggered the onset of Harada disease in TB endemic country like Nepal leading to simultaneous presentation of Tubercular Harada Disease.

1. Introduction

Tuberculosis (TB) is a severe multi-systemic disease caused by *Mycobacterium tuberculosis* (MTB) and is one of the leading infectious cause of morbidity and mortality worldwide [1]. Worldwide, TB is the 13th leading cause of death and the second leading infectious killer after COVID-19. In 2020, an estimated 10 million people fell ill with tuberculosis (TB) worldwide with 1.4 million TB deaths. Over 95% of cases and deaths are in developing countries 2]. This symbolizes the lack of adequate funding for TB prevention, diagnosis, treatment and care with a major global economic and health burden [2]. Thus, it is the commonest infectious etiology in developing world especially in the south asian countries. In Nepal, it remains a major public health program causing around 7000 deaths annually [3]. Ocular involvement is considered as a relatively uncommon extrapulmonary manifestation of TB and can present as a vision-threatening condition [3]. Tuberculous uveitis (TBU) is granulomatous and a great mimicker of various uveitis entities and it should be considered in the differential diagnosis of any type of intraocular inflammation especially in the TB endemic country like Nepal.

On the other hand, Vogt Koyanagi Harada Disease (VKHD) is also an important cause of granulomatous panuveitis with iridocyclitis, vitritis, exudative retinal detachments, diffuse choroidal swelling, and optic disc hyperemia [4]. It is multisystemic autoimmune disorder, often associated with neurologic and cutaneous manifestations [5]. Sometimes, can manifest as Harada's disease where ocular findings exit in absence of systemic features.

Since, both uveitis present in the form of granulomatous uveitis, it becomes a diagnostic and therapeutic challenge for the ophthalmologist in this part of the world to plan the management. TBU, being the infective entity warrants antimicrobial treatment with anti tubercular therapy (ATT) but VKHD is an immunological entity so needs an initial high dosage of corticosteroids followed by long-term immunosuppressants [6]. Surprisingly, there occurs situation where both uveitic entities can present together and the treatment regimens needs to be assimilated for both infective and immunological aspects.

* Corresponding author.
E-mail addresses: helloranju50@gmail.com (R. Kharel Sitaula), 0211preeti@gmail.com (P. Agrawal).

https://doi.org/10.1016/j.amsu.2022.104294
Received 24 May 2022; Received in revised form 24 July 2022; Accepted 26 July 2022
Available online 31 July 2022

Thus, midst of this conundrum, we aim to report two cases of panuveitis with the mixed features of tubercular uveitis and Harada disease which were successfully managed with the ATT and immunosuppressant. Thereby, this study highlights the chances of simultaneous occurrence of infectious and non-infectious cause of panuveitis in patients of TB endemic region. Thus, screening of latent TB in every VKHD cases would be worthwhile before the start of any immunosuppressant in TB endemic regions. Written informed consent was obtained from the patient for publication of this case report and accompanying images and this report adheres with the guideline of SCARE 2020 [7].

2. Case – 1

A 30-year-immunocompetent male presented with progressive diminution of vision in both eyes for 3 months with minimal pain. He had no history of skin rashes, headache, weight loss, cough, hair loss, ear and neurological symptoms systemic illness in his family.

On ocular examination, his Best Corrected Visual Acuity (BCVA) in right eye (RE) was 6/36, N12 and left eye (LE) was 6/12, N8. RE had quiet anterior chamber with normal pupillary reflex but LE had 0.5+ cells in anterior chamber with sectoral posterior synechia and sluggish pupillary reaction. Trace cells in posterior vitreous were present in both eyes with 2+ vitreous haze. Right fundus showed hyperemic edematous disc with macular star. Peripheral phlebitis with pigmentary changes was present in all quadrants (Fig. 1A). The Left fundus showed paramacular choroiditis with few chorio-retinal scars, pigmentary changes, edematous disc and dull foveal reflex (Fig. 1B). The retinal vessels were normal in both eyes. The sunset glow was present in both fundus.

USG B-scan of left eye showed hyperechoic shadows in vitreous persisting in high and low gain; suggestive of retinal detachment. T Sign was absent. Optical coherence tomography (OCT) of both eyes confirmed increased central macular thickness, optic disc swelling, thickened choroid along with areas of exudative macular detachment in LE (Fig. 1C).

Baseline blood investigations were normal. Serological tests like HIV/HBV, HCV, TPHA were negative. ESR and CRP were not raised and serum ACE was normal. The chest X-ray was also normal. Tuberculin skin test was positive with a non necrotic induration of 16 mm diameter (Fig. 1D) which was supported with positive TB QuantiFERON Gold test. Polymerase chain reaction analysis of the ocular fluid could not be performed due to unavailability at our set up. Electroretinogram (ERG) of both eyes showed reduced P1 wave amplitude (Fig. 1E and F).

The features of bilateral choroiditis, disc edema, macular edema and serous retinal detachment with sunset glow fundus with no systemic features were supportive of Harada's disease. But the positive tubercular skin test (TST) and quantiFERON TB Gold test for immune gamma release assay (IGRA) was suggestive of presumed ocular tuberculosis. So the diagnosis of Tubercular Harada's disease was done and after physician consultation, he was started with intravenous methylprednisolone at 1000mg/day for 3 days followed by oral corticosteroid 1mg/kg/day alongwith CAT- I ATT regimen (2HRZE + 7 HR) and oral azathioprine 500mg twice. The patient was kept under close observation.

On 1 month follow up, the disc edema, macular edema and serous retinal detachment got resolved in both eyes. The chorioditis also reduced with areas of pigmentary mottling, subretinal fibrous strands and sunset glow fundus (Fig. 1F&G).

His oral steroids were tapered off by 3 months, completed 9 months of ATT and presently he is under oral azathioprine 500mg maintenance dose. His vision in both eyes is 6/6, N8, fundus has sunset glow but no evidence of recurrence of uveitis is noted in the last 2 years follow up.

3. Case 2

A 51 year-old immunocompetent female presented with bilateral diminution of vision since 3 months, associated with mild pain, redness and floaters on/off. The BCVA was 6/18, N8 and 6/24, N12 in right and left eye respectively. Anterior segment examination revealed 0.5+ cells with posterior synechiae at 3, 9 and 11 o'clock position in RE. The LE had 1+ cells in the anterior chamber with 1+ vitreous cells. The vitreous haze of 2+ was noted bilaterally.

Both fundus had sunset glow with edematous disc, subtle serous detachment and multifocal choroiditis (Fig. 2A and B). The FFA showed early hypofluorescence (Fig. 2C and D) with late hyperflourescence

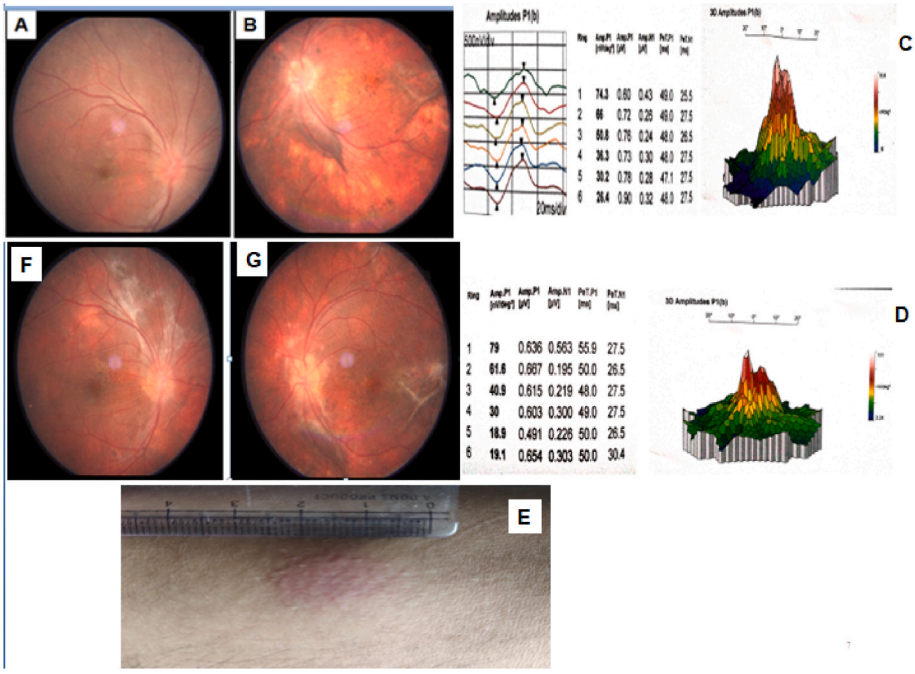

Fig. 1. The fundus picture at presentation showing disc edema, peripapillary edema with macular star in RE (A) and sunset glow with multifocal chorioditis and pigmentary retinal changes in LE (B). The P1 wave amplitude was reduced in both RE (C) and LE (D). After treatment, the retinal edema and chorioditis resolved; both the eyes had sunset glow with sub-retinal fibrosis and dull FR (E) and (F).

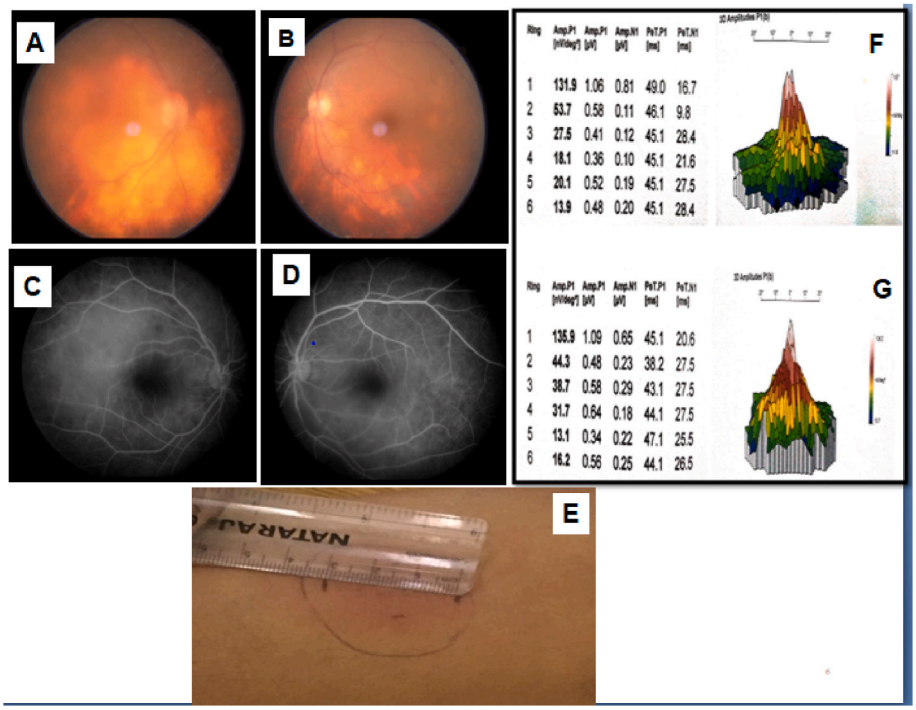

Fig. 2. The fundus picture at presentation showing the sunset glow with disc edema, multifocal choroiditis along with serous RD in RE (2A) and LE (2B). The early hypoflourescence was noted in the FFA (2C & 2D). The mantoux test showed indurated area of 28 mm in the arm (2E). And normal amplitude and latency were noted after inititation o f the treatment in the RE (2F) and LE (2G).

along with staining and pin point leakage. The OCT confirmed the macular edema in RE.

Baseline blood parameters were normal and the serological tests for HIV, Hep B/C, TPHA were negative. ESR, CRP and serum ACE were within the normal limits. Though the chest x-ray was normal, the tuberculin skin test was positive with a non necrotic induration of 28 mm diameter (Fig. 2E). And subsequent, TB quantiFERON Gold test was also positive. So, she was diagnosed as Tubercular Harada disease.

Physician started her on ATT (2 HRZE +7 HR) along with tapering dose of oral corticosteroid (1mg/kg/day) with oral methotrexate 15mg/week. After 15 days, her choroidal lesions and disc edema started decreasing. The ERG performed at this stage had normal P1 wave amplitude (Fig. 2F and G).

By 3rd month, subretinal fibrosis developed with peripapillary atrophy, pigmentary mottling and sunset glow fundus. Her oral steroid was stopped by 3 months and 9 months of ATT was completed. She was kept oral methotrexate maintenance dose of 10mg/week for 2 years. She developed steroid induced posterior subscapsular cataract and her BCVA was 6/18, N8 and LE 6/36, N8. Subsequently she underwent cataract surgery on both eyes after and had 6/6, N8 visual acuity in both eyes. No recurrences of ocular symptoms have been noted and she has been under our follow up since last 4 years.

4. Discussion

VKHD is a granulomatous autoimmune inflammatory condition mediated by T lymphocytes that target melanocytes [8,9]. These activated T cells most likely initiate the inflammatory process through the generation of cytokines, IL 17 and IL 23, 35 in individuals with altered tolerance to melanocytes from deficient T regulatory cells [10]. The exact trigger that induces altered tolerance to melanocytes is still not known. But, genetic susceptible person expressing HLA DRB1*0405, combined with viral infection (CMV, EBV) are thought to initiate the autoimmune process [11–13].

In our cases, we presume that there could have been a cross-reaction between the tyrosinase peptide and the mycobacterium peptide, hypothesizing that perhaps VKHD could develop in patients from molecular mimicry after infection with TB. In TB endemic country like Nepal, the tubercle bacilli may remain in a dormant phase in the retinal pigment epithelium (RPE). Under certain circumstances, these bacilli get favourable environment to induce uveal inflammation as well as act as the trigger for the initiation of immunological cascades in the ocular melanocytes of VKHD suspectibility people. Or on the other hand, our population have high chance of having latent TB, and upon the start of immunosuppressants, there could be high chance of reactivation of latent to active form of TB. Thus, there are both possibilities of tuberculosis bacteria trigerring the VKHD entity or VKHD treatment drugs activation the latent TB in our part of region.

Nepal lies within TB suspectible region and we report two cases where ocular Tb and VKHD got manifested at the same time. The clinical features were suggestive of presumed ocular tuberculosis as well as Harada's component of VKHD but the laboratory features like positive mantoux and positive IGRA test supported the presence of mycobacterium infection. Both VKHD and ocular TB share common features of granulomatous ocular inflammation, and could affect the eyes at the same time in absence of the systemic features in Tb endemic country like ours. We put forward the term "Tubercular Harada disease" (TBHD) in such condition and recommend the simultaneous use of the ATT, oral corticosteroid and immunosuppressant to combat the ocular morbidities. Although all our population are vaccinated at childhood with BCG, the tuberculin skin test was strongly positive in both these cases and was supported by the positive IGRA result.

There had been earlier reports on the reactivation or secondary infection of mycobacterium tuberculosis, occurrence of tubercular granulomas with the use of drugs that causes immunosuppression [14–16]. Herein, VKHD and Behcets' disease occurred first and later the immunosuppressants used for their treatment caused the occurrence of ocular tuberculosis. It's a known fact that the use of immunosuppressant raises the risk of opportunistic infections which can be bacterial or viral since it causes immunological derangement in Natural Killer cells, CD-4,

and CD-8 cells [16,17]. We found another report on a rare case of bilateral asymmetrical tuberculous sclero-uveitis presenting as a Vogt-Koyanagi-Harada (VKHD)-like/serpiginous-like TB uveitis [18]. Moreover, a recent case highlighted the diagnostic dilemma between VKHD and TB, and the possibility of reactivation of latent TB on immunosuppression. The presence of underlying latent TB in that case was attempted with extensive investigations, but this VKHD patient developed neurotuberculosis within 2 months, creating perplexity of diagnosis between two granulomatous conditions –VKHD and TB in India which is also Tb endemic zone like Nepal [19].

Thus, many times, the features of VKHD and ocular Tb become indistinguishable in our part of the world. All these clinical findings may be indicative, but not pathognomonic for this disease. So, diagnostic conundrum can arouse between these two ocular conditions. On top of it, there is no single definitive laboratory test to confirm both conditions. However, it's the precise clinical evaluation that can aid to sort out the conditions clinically.

We admit that we could neither perform HLA DR & DQ haplotyping to assess the genetic suspectibility for VKHD among our patients, nor we could perform the ocular fluid PCR analysis to detect the mycobacterium bacilli in the ocular sample in these cases. But absence of the positivity of HLA D haplotype & ocular fluid Tb PCR does not rule out the disease in presence of strong clinical suspicion. Both these tests are unavailable at our settings hence were not performed.

The aim of this report is to pave future path to work upon the hypothesis that mycobacterium could trigger the tryosinase peptide antigen which is the target of autoimmunity by T lymphocytes. We purpose that there could be a cross-reaction between the tyrosinase peptide and the mycobacterium peptide leading to the stimulation and significant proliferation of immune cascades in VKHD receptive patients. The major limitation of this report is the limited patient numbers and thus further studies are required to affirm this relationship between VKHD and Tb in this part of the world. Prompt recognition along with early initiation of anti-tubercular therapy is warranted in such cases along with steroid and immunosuppressant.

5. Conclusion

The diagnosis and treatment are both challenging because VKHD disease and TB can share the similar manifestation of uveitis but require different treatments. Our cases reveal an atypical manifestation of tubercular uveitis with Harada disease, emphasizing the fact that tubercular Harada disease is a very rare condition yet possible cause of posterior uveitis in our part of world.

Ignoring the role of mycobacterium in VKHD patients and starting the treatment with mere steroid and immunosuppressants, may lead to the recurrent bouts of uveitic attacks. Diagnostic approach is challenging and calls for early diagnosis and prompt treatment, as it can potentially lead to blindness.

Ethical approval

Ethical approval from the Institutional Review Committee of Institute has been obtained to proceed with the current publication.

Source of funding

There are no funding sources to be declared.

Author contribution

Ranju Kharel Sitaula made substantial contributions to management of the case, conception and design of the manuscript, acquisition of data, analysis and interpretation of data; she has been involved in drafting the manuscript and revising it critically for important intellectual content. Preeti Agarwal have made substantial contributions to interpretation of data and have been involved in drafting the manuscript and revising it critically for important intellectual content.

Trail registry number

None.

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 on request.

Garantor

Ranju Kharel Sitaula.

Patient consent

Written informed consent was obtained from the patient for the publication of this case report.

Provenance and peer review

This article was not commissioned and was peer reviewed.

Declaration of competing interest

The authors declare that they have no conflict of interest regarding the publication of this case report.

References

[1] D. Maher, The Global Epidemic of Tuberculosis: a World Health Organization Perspective, Mycobacterial infections, 1999.
[2] J. Chakaya, et al., Global tuberculosis report 2020–reflections on the global TB burden, treatment and prevention efforts, Int. J. Infect. Dis. 113 (2021) S7–S12.
[3] R.V. Alvarez Gg, W. Hodge, Ocular tuberculosis: diagnostic and treatment challenges, Int. J. Infect. Dis. : IJID : official 603 publication of the International Society for Infectious Diseases. 13 (4) (2009) 432–435.
[4] A. Neves, et al., Unilateral Vogt-Koyanagi-Harada disease: a clinical case report, Case reports in ophthalmology 6 (3) (2015) 361–365.
[5] L. Du, A. Kijlstra, P. Yang, Vogt-Koyanagi-Harada disease: novel insights into pathophysiology, diagnosis and treatment, Prog. Retin. Eye Res. 52 (2016) 84–111.
[6] R.S. Moorthy, H. Inomata, N.A. Rao, Vogt-koyanagi-harada syndrome, Surv. Ophthalmol. 39 (4) (1995) 265–292.
[7] R.A. Agha, et al., The SCARE 2020 guideline: updating consensus surgical CAse REport (SCARE) guidelines, Int. J. Surg. 84 (2020) 226–230.
[8] K. Norose, A. Yano, Melanoma specific Th1 cytotoxic T lymphocyte lines in Vogt-Koyanagi-Harada disease, Br. J. Ophthalmol. 80 (11) (1996) 1002–1008.
[9] S. Sugita, et al., Melanocyte lysis by cytotoxic T lymphocytes recognizing the MART-1 melanoma antigen in HLA-A2 patients with Vogt–Koyanagi–Harada disease, Int. Immunol. 8 (5) (1996) 799–803.
[10] L. Chen, et al., Diminished frequency and function of CD4+ CD25high regulatory T cells associated with active uveitis in Vogt-Koyanagi-Harada syndrome, Investig. Ophthalmol. Vis. Sci. 49 (8) (2008) 3475–3482.
[11] F.M. Damico, et al., T-cell recognition and cytokine profile induced by melanocyte epitopes in patients with HLA-DRB1* 0405-positive and-negative Vogt-Koyanagi-Harada uveitis, Investig. Ophthalmol. Vis. Sci. 46 (7) (2005) 2465–2471.
[12] S. Sugita, et al., Cross-reaction between tyrosinase peptides and cytomegalovirus antigen by T cells from patients with Vogt-Koyanagi-Harada disease, Int. Ophthalmol. 27 (2) (2007) 87–95.
[13] N. Usui, Detection of Epstein-Barr virus DNA by the polymerase chain reaction in cerebrospinal fluid from patients with Vogt-Koyanagi-Harada disease, in: Proceedings of the 3rd International Symposium on Uveitis, Kugler Publ, 1992, 1992.
[14] T.-W. Qian, S.-Q. Yu, X. Xu, A challenging case of tuberculosis-associated uveitis after corticosteroid treatment for Vogt-Koyanagi-Harada disease, Int. J. Ophthalmol. 11 (8) (2018) 1430.
[15] L. Atmaca, F.N. Yalçindağ, A. Çiledağ, Choroidal tuberculoma in a patient with ocular Behcet disease, Int. Ophthalmol. 32 (1) (2012) 93–96.
[16] P. Bajgai, A. Sharma, R. Singh, Disseminated tubercular granulomas associated with the use of azathioprine, Ocul. Immunol. Inflamm. (2019) 1–5.

[17] R.M. Weinshilboum, S.L. Sladek, Mercaptopurine pharmacogenetics: monogenic inheritance of erythrocyte thiopurine methyltransferase activity, Am. J. Hum. Genet. 32 (5) (1980) 651.

[18] D. Kalogeropoulos, et al., Tuberculous posterior sclero-uveitis with features of Vogt-Koyanagi-Harada uveitis: an unusual case, Am. J. Case Rep. 18 (2017) 367.

[19] R. Rasheed, et al., A perplexing case of bilateral Vogt-Koyanagi-Harada syndrome, Indian J. Ophthalmol. Case Rep. 2 (1) (2022) 120.