Vernal keratoconjunctivitis in human immunodeficiency virus – The possible role of T-helper 1–T-helper 2 shift

Shweta Agarwal, Bhaskar Srinivasan, Geetha Iyer, Sridharan Sudharshan[1], Kavita Kalaivani[2]

Human immunodeficiency virus infection (HIV) is associated with a reduced T-helper (Th) 1 response, and vernal keratoconjunctivitis (VKC) occurs secondary to a heightened Th2 response. VKC has been reported to occur in patients with HIV. In all probability, a Th1–Th2 shift occurs in the immune response in progressive HIV patients with a decreasing CD4 count. This shift could be the probable cause for the initiation and gradual worsening of the VKC in our patient that corresponded to the dropping CD4 counts. VKC resolved only after a change in antiretroviral therapy for HIV that caused a demonstrable increase in the CD4 counts possibly by reversing the shift.

Key words: Allergic conjunctivitis, human immunodeficiency virus, vernal keratoconjunctivitis

Human immunodeficiency virus (HIV) causes HIV infection which progresses to acquired immunodeficiency syndrome in advanced cases with a severely suppressed immune state secondary to decreasing CD4 cell counts. HIV infects primarily cells in immune system such as T-helper (Th) cells (CD4), macrophages, and dendritic cells, leading to progressive failure of the immune system, which predisposes to opportunistic infections and cancers.

The ocular manifestations in HIV correlate with the immune status. CD4 count >500 cells/μl are associated with molluscum contagiosum and Kaposi's sarcoma and <200 cells/μl with ocular tuberculosis.[1,2] The anterior-segment complications include infections such as molluscum contagiosum (5%–15%), herpes zoster (5%–15%), tumors such as Kaposi's sarcoma (20%–25%), blepharitis, dry eye (20%), allergic conjunctivitis (5%–21%), and uveitis.[2,3]

Vernal keratoconjunctivitis (VKC) is a chronic and severe form of ocular allergy characterized by the involvement of mast cells, T-cells, eosinophils, neutrophils, and macrophages. Increased expression of Th2 cells and its cytokines has been described in conjunctiva of VKC patients.[4]

The pathophysiology of HIV implicates a decrease in CD4+ cell counts, leading to an immunodeficient state. In the chronic nonprogressive or on treatment stage, the CD4+ Th1 cells play an important role in maintaining a specific antiviral response with the aim of treatment being to reverse the immunodeficient stage. The Th2 response in HIV infection could either be suppressed or normal (relatively dominant compared to the Th1 response) depending on the stage of the disease with a reported distinct Th1–Th2 shift in advanced disease process with significantly low CD4+ counts although very few studies do not concur with the same.[5]

This shift with the progression of HIV infection can lead to increased levels of total serum IgE.[6] Raised IgE and Th2 predominance can result in allergic predisposition in these patients.

Allergic conjunctivitis and vernal catarrh have been reported as one of the anterior-segment manifestations in HIV though the exact etiology of the same in HIV-infected individuals has not been clearly elucidated.

We herein report a case of a child with HIV with refractory VKC which supports the Th1–Th2 shift hypothesis in advanced disease, thus highlighting the need to be aware of this possibility and manage them appropriately.

Case Report

A 9-year-old HIV-infected child since birth on highly active antiretroviral therapy (HAART) presented with a history of recurrent redness and itching for the past 5 months with no other systemic ailments. CD4 counts had dropped from a baseline of 1145 cells/μl to 467 at 5 months back. His best-corrected visual acuity (BCVA) was 6/18 in the right eye and 6/12 in the left, with early mild punctate epitheliopathy and posterior subcapsular cataract in both eyes. The rest of the ocular examination was within normal limits. There was no history suggestive of an allergic diathesis. He was diagnosed with allergic conjunctivitis and was initiated on olopatadine 0.2% eye drop once/day and lubricants.

Access this article online

Quick Response Code:

Website: www.ijo.in

DOI: 10.4103/ijo.IJO_76_18

CJ Shah Cornea Services/Dr G Sitalakshmi Memorial Clinic For Ocular Surface Disorders, Medical Research Foundation, Sankara Nethralaya, [1]Department of Uvea, Medical Research Foundation, Sankara Nethralaya, [2]Department of Paediatric Ophthalmology and Strabismus, Sankara Nethralaya, Chennai, Tamil Nadu, India

Correspondence to: Dr. Bhaskar Srinivasan, CJ Shah Cornea Services/Dr G Sitalakshmi Memorial Clinic For Ocular Surface Disorders, Medical Research Foundation, Sankara Nethralaya, 18 College Road, Chennai - 600 006, Tamil Nadu, India. E-mail: drbhaskar@hotmail.com

Manuscript received: 15.01.18; Revision accepted: 15.04.18

Cite this article as: Agarwal S, Srinivasan B, Iyer G, Sudharshan S, Kalaivani K. Vernal keratoconjunctivitis in human immunodeficiency virus – The possible role of T-helper 1–T-helper 2 shift. Indian J Ophthalmol 2018;66:1004-6.

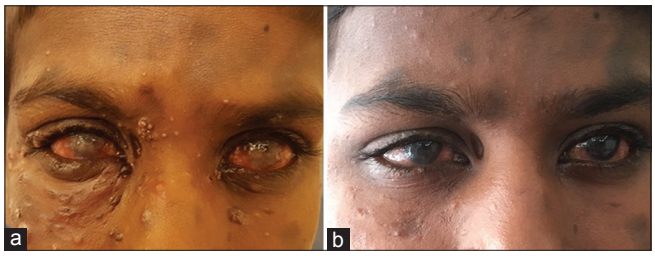

Figure 1: (a) Both eyes showing active vernal keratoconjunctivitis with partial limbal stem cell deficiency and molluscum contagiosum on the lids and face with a fall of CD4 count to 200 cells/μl. (b) Eyes quiet with resolved molluscum contagiosum after change of highly active antiretroviral therapy and improvement of CD4 counts to 399 cells/μl

A month later, the child presented with worsening of symptoms along with Horner Trantas dots, severe diffuse punctate epitheliopathy, and grade 2 tarsal papillae. Topical fluorometholone 4 times/day and cyclosporine 2% eye drops 2 times/day were added.

Over a period of 4 months, the cataract progressed with a drop in vision to 6/60 in both eyes with not much improvement in the allergic status of the eye. Prednisolone acetate 1% eye drop was instituted 4 times a day in attempt to reduce the allergy before cataract surgery, which was performed sequentially a month later in both eyes.

Although the allergy appeared to have abated in the perioperative period, it continued to worsen with a constant need for prednisolone acetate over 8 months with constant intraocular pressure monitoring, and hence, tacrolimus eye ointment 0.03% 2 times/day was started. His allergy however continued to worsen with features suggestive of limbal stem cell deficiency.

During this same time, he developed severe molluscum contagiosum infection over the face, and his CD4 counts were noted to have dropped to 200. He was started on the second line of HAART and antituberculous drugs. Gradually, as his CD4 counts improved to 399, the molluscum infection resolved with resolution of the allergy in the eye without the need for topical steroids [Figs. 1 and 2].

At the last follow-up, he was completely off steroids for 3 months, with a BCVA of 6/24 in both eyes. He was advised to continue tacrolimus ointment 0.03% 2 times/day, olopatadine, and lubricants. The CD4 counts at the last visit were 418 cells/μl.

Discussion

The immune response to any presenting antigen is either cell-mediated or humoral type which is based on the cytokine production by the Th CD4 cells.[7] The Th1/Th2 balance regulates the class of immune response in health and disease.

HIV primarily infects CD4+ (Th1) cells with many reports describing a switch from Th1–Th2 response, which correlates with the disease progression in patients with HIV.[8,9]

Whether a preferential replication of the HIV-1 in Th1 CD4+ cells, an upregulation of the cytokines that lead to a Th2 response, or a downregulation of cytokines that induce a Th1 response cause the Th1–Th2 shift is not yet known, though the same has been seen to occur with severely low CD4 counts.[9,10]

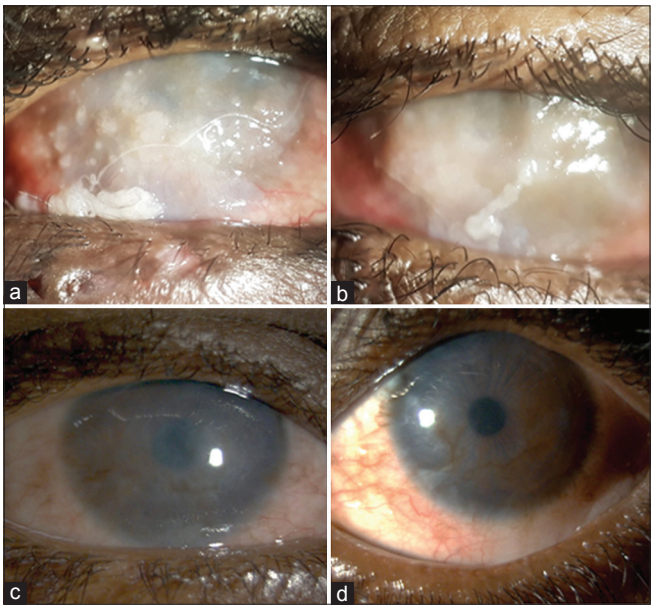

Figure 2: (a and b) Both eyes showing active vernal keratoconjunctivitis with corneal haze after a fall of CD4 counts to 200 cells/μl. (c and d) Both eyes quiet with relative clearing of the cornea after resolution of vernal keratoconjunctivitis following improvement of CD4 counts to 399 cells/μl

Classically, in our case, the child was asymptomatic when the CD4 counts were high, with emergence of ocular allergy concurring with a drop in counts along with infection by molluscum contagiosum on further worsening of the counts. This case is therefore probably representative of the possible hypothesis of Th1–Th2 switch during HIV disease. Whether the heightened Th2 response with reduced CD4 counts responsible for ocular allergy would be refractory to routine management of vernal catarrh with potent steroids as was seen in our case is not known. What was of further interest was the resolution of allergy with an improvement in counts.

Conclusion

This case, therefore, from an ophthalmologist's point of view, highlights the need to be aware of the correlation between heightened allergic response and progression of HIV disease with decreasing CD4 counts due to the Th1–Th2 shift that might be refractory to routine management. Initiating systemic steroids or immunosuppression as is usually done in refractory VKC is not recommended here due to the already immunocompromised state. More effective antiretroviral therapy might be indicated in such cases to improve the CD4+ counts that would subsequently reverse the Th1–Th2 shift alleviating the effects of Th2 dominance.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient's mother has given the consent for his images and other clinical information to be reported in the journal. The patient's mother understands that his name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Cunningham ET Jr., Margolis TP. Ocular manifestations of HIV infection. N Engl J Med 1998;339:236-44.
2. Martin-Odoom A, Bonney EY, Opoku DK. Ocular complications in HIV positive patients on antiretroviral therapy in Ghana. BMC Ophthalmol 2016;16:134.
3. Jeng BH, Holland GN, Lowder CY, Deegan WF 3rd, Raizman MB, Meisler DM, *et al.* Anterior segment and external ocular disorders associated with human immunodeficiency virus disease. Surv Ophthalmol 2007;52:329-68.
4. Leonardi A, De Dominicis C, Motterle L. Immunopathogenesis of ocular allergy: A schematic approach to different clinical entities. Curr Opin Allergy Clin Immunol 2007;7:429-35.
5. Clerici M, Shearer GM. A TH1–TH2 switch is a critical step in the etiology of HIV infection. Immunol Today 1993;14:107-11.
6. Viganó A, Principi N, Crupi L, Onorato J, Vincenzo ZG, Salvaggio A, *et al.* Elevation of IgE in HIV-infected children and its correlation with the progression of disease. J Allergy Clin Immunol 1995;95:627-32.
7. Mosmann TR, Coffman RL. TH1 and TH2 cells: Different patterns of lymphokine secretion lead to different functional properties. Annu Rev Immunol 1989;7:145-73.
8. Ramalingam S, Kannangai R, Vijayakumar TS, Mathai D, Abraham OC, Subramanian S, *et al.* Subtype and cytokine profiles of HIV infected individuals from South India. Indian J Med Res 2005;121:226-34.
9. Clerici M, Fusi ML, Ruzzante S, Piconi S, Biasin M, Arienti D, *et al.* Type 1 and type 2 cytokines in HIV infection – A possible role in apoptosis and disease progression. Ann Med 1997;29:185-8.
10. Gorenec L, Zidovec Lepej S, Grgic I, Planinic A, Iscic Bes J, Vince A, *et al.* The comparison of Th1, Th2, Th9, Th17 and Th22 cytokine profiles in acute and chronic HIV-1 infection. Microb Pathog 2016;97:125-30.