



CYTOMEGALOVIRUS RETINITIS WITH OCCLUSIVE VASCULITIS IN BOTH EYES OF IMMUNOCOMPETENT MALE PATIENT

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ABSTRACT

Purpose : To report a case of cytomegalovirus retinitis with occlusive vasculitis in both eyes of an immunocompetent male patient.

Methods: A 48 year old male patient on treatment for aseptic meningitis presented to the ophthalmology department with sudden bilateral painful diminution of vision. Ophthalmologic examination showed anterior segment inflammation with mild vitreous reaction and focal retinitis patches bilaterally with left eye also showing signs of optic nerve head edema and macular edema. Patient was started on IV and topical steroids (prednisolone). Extensive diagnostic workup was performed including Fluorescein angiography, serology for infectious agents like tuberculosis, HIV and syphilis which were negative. In spite of treatment, patient's vision was gradually deteriorating when aqueous tap was done and patient was empirically started on injection acyclovir 500 mg TID and later continued with oral steroids and acyclovir. Topical steroids and homatropine was continued. Intravitreal Ranibizumab was given to halt the retinal inflammation. Subsequent follow ups showed resolving retinal inflammation with extensive sclerosis & attenuation of the retinal arteries.

Results : In spite of treatment with high dose iv methylprednisolone, injection acyclovir, topical steroids and Intravitreal lucentis, patient had significantly decreased vision due to occlusive vasculitis.

Conclusion: Cytomegalovirus infection can be associated with occlusive vasculopathy in immunocompetent individuals.

KEYWORDS : Cytomegalovirus retinitis, immunocompetent, occlusive vasculitis

Introduction

Cytomegalovirus (CMV) retinitis is commonly seen in immunocompromised patients. Most commonly affected are the patients with AIDS whose CD4 cell count less than 50/ μ L¹, patients on long-term immunosuppression² and neonates.

With the advent of highly active retroviral therapy for AIDS, Cytomegalovirus retinitis has significantly reduced by 75%^{1,3} Following primary infection, CMV disseminates hematogenously and may infect the retina and other areas of the central nervous system⁴

Case Report

A 48 year old male patient was referred from Medicine to the department of Ophthalmology with complaints of sudden onset of poor vision in left eye more than right eye, less than 1 day. There was no other significant systemic localizing symptoms with the present complaints, including trauma, vomiting and convulsions. He had no past history of Diabetes Mellitus, Hypertension, Tuberculosis, Bronchial Asthma, Epilepsy. On examination

GENERAL PHYSICAL EXAMINATION

Middle aged patient who is moderately built and nourished conscious cooperative well oriented to time, place and person.

Pulse rate- 86bpm
BP – 122/70 mmHg

SYSTEMIC EXAMINATION

1. Cardiac - S1 S2 heard no murmurs
2. Respiratory - B/L NVBS heard
3. Per abdomen - Soft, no organomegaly
4. Central nervous System – Higher mental Functions - normal, Neck rigidity- Present No focal neurological deficits With a working diagnosis of meningitis, Patient was started on Inj. Ceftriaxone 2gm iv bid, paracetamol, pantoprazole.

The diagnosis was revised as aseptic meningitis, Inj. Meropenam IV BD started was started on day 6 (was given for 2 weeks). Patient

complained of pain and redness in both eyes for which Ophthalmology opinion was taken- diagnosed as anterior uveitis, Prednisolone eye drops were prescribed.

Investigations:-

TC- 25000, Serial Total counts showed decline 19,000 – day 3, 14,500 – day 5.

ESR-35mm/hr, CRP-1:4, 2.4mg/ml, RA factor-negative.

Renal function tests, Coagulation profile- Normal
Dengue NS 1, IgM/ IgG, WIDAL, Typhi dot, Malaria Ag.- NEGATIVE
S. calcium -9.3mg/dl, s. phosphorus-3.6mg/dl.

ANA- cANCA, pANCA - negative,
VDRL, HIV, RA, Mantoux, - Negative
LFT- ALP- 440 IU/ML, GGT-304 IU/ML,
USG abdomen and pelvis - normal
Lumbar puncture was done- CSF analysis - Biochemistry- glucose- 58mg/dl, protein- 130mg/dl(N-40), LDH – 31U/L, Cytology- gross clear and colorless, 18cells/mm³, 100%lymphocytes, no atypical cells.

Screening – ECHO showed LVEF- 58%, no RWMA CT brain - Normal.

With deteriorating vision, patient was re-evaluated at Ophthalmology department, Visual acuity Right eye (RE)- 6/36, Left eye (LE)- CF@1m, pupillary reaction was sluggish, AC- flare 2+, cells 2+ in both eyes. Upon dilation, vitreous reaction was minimal in both eyes. Right eye showed areas of focal retinitis in zone 2, disc appeared normal. Left eye showed optic nerve head edema, retinitis and macular edema – zone 1 involvement. There were few cotton wool spots in the LE. No haemorrhages were noted.

Clinical diagnosis of CMV Neuro retinitis was made, patient was started on Inj. Methyl prednisolone in 100 ml NS over 30 mins. Aqueous tap was done – PCR for VZV, CMV, HSV I & II - negative. With further deterioration of vision, patient was empirically started on inj. Acyclovir 500mg in 100 ml NS TID and 5 days later, it was switched to oral Antiviral – Acyclovir 800mg, 5 times a day and oral steroids - wisolone 60 mg OD was started for 2 weeks. Topically, prednisolone and homatropine eye drops were continued.

Follow up examination – patchy retinitis in zone 1 & zone 2 BE with retinal haemorrhages, sheathing of the retinal vessels . Vitreous reaction was limited to anterior vitreous cells in both eyes. Fluorescein angiography - staining & leakage from vessels in ZONE 1 & 2 with extensive areas of CNP in both eyes.

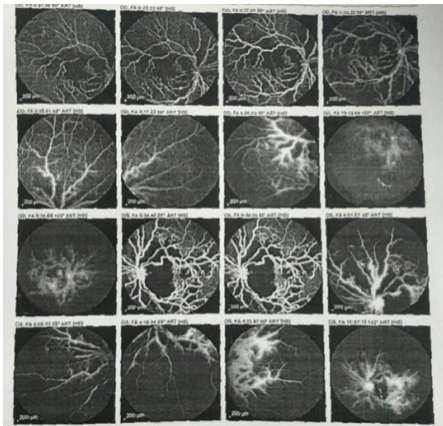
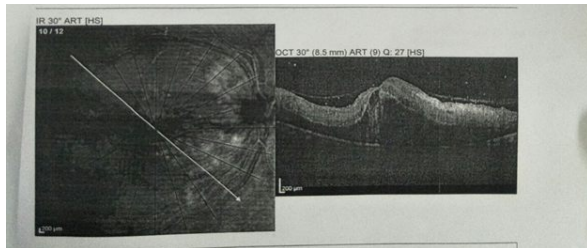


Figure 1: Fluorescein angiogram showing staining and leakage from vessels in ZONE 1 & 2 with extensive areas of CNP in both eyes.

OD



OS

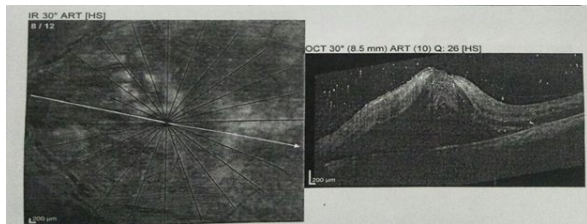


Figure2: (A)(B) Optical Coherence Tomography at the fovea demonstrating extensive macular edema in both eyes.

Intravitreal Ranibizumab was given to both eyes with the hope of halting the relentless retinal inflammation in both eyes. 2 weeks later retinitis showed signs of resolution with healing retinitis. The retinal arteries showed extensive sclerosis and attenuation.

ZONE 1 - 1DD surrounding the disc, 2 DD around the fovea- sight threatening;

ZONE 2 –Anterior to zone 1 & posterior to Vortex vein ampullae

ZONE 3 – posterior to Zone 2

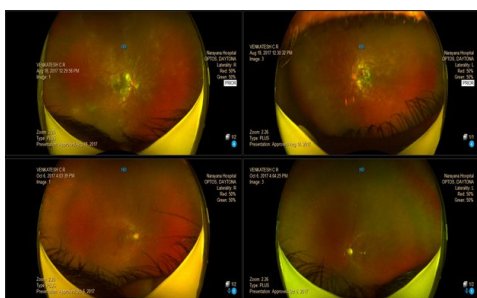


Figure 3: Color fundus photograph demonstrating healing retinitis and extensive sclerosis and attenuation of the vasculature.

Subsequent follow ups showed resolving anterior segment inflammation and retinitis with tortuous attenuated vessels throughout the retina and few macular exudates. However no improvement in vision was noted . Last followup vision was CF-CF in both eyes.

DISCUSSION

CMV retinitis was a rare disease in the pre AIDS era, seen only in congenital CMV infections & in transplant recipients. With the understanding of the disease spectrum of AIDS, it became evident that CMV retinitis typically occurred in 80% of the patients with AIDS –CMV disease ,when CD4 counts fell below 50^{5,6}.

In immunocompetent hosts, acquired CMV infection manifests as a mild self limited , flu like illness followed by a latent infection in granulocytes. The viral proteins prevent the conjunction with HLA class I molecules & destruction by CD8+ T cells. CMV infected cells evade NK cell surveillance. Majority of the patients with newly diagnosed retinitis have evidence of systemic CMV infection/replication⁷

The retinitis is primarily due to the infection of vascular endothelial cells⁸. The retinitis causes full thickness retinal necrosis & retinal destruction. The lesions spread contiguously, involving the fovea & optic nerve with permanent visual loss⁹.

In AIDS – CMV spectrum necrotic retinitis with damage to fovea & optic nerve, retinal detachment & in the HAART era cataract has been noted as the leading cause of visual loss.

Visual loss in patients with AIDS -cytomegalovirus retinitis managed with HAART showed macular edema particularly with Immune recovery uveitis¹⁰.

The case reported here had anterior uveitis , retinitis with vasculitis and macular edema. The cotton wool spots & occlusive vasculitis without any evidence of HIV or CMV infection, posed a diagnostic dilemma .

In a retrospective study of 113 eyes with retinal vasculitis in eastern India, capillary nonperfusion was the most common fundus fluorescence angiography (FFA) finding which was found in 40% of the cases, followed by collateral vessels, seen in 19.5% of eyes with vasculitis. All major causes of retinal vasculitis such as collagen vascular diseases, systemic granulomatous diseases were ruled out. Although there is no proven cause effect relationship between different types of retinal vasculitis & ischemia, the commonly indicated etiologies include Tuberculous retinal vasculitis, Behcet's syndrome, sarcoidosis and multiple sclerosis¹¹.

The pathogenesis of ischemia in retinal vasculitis may be due to thrombotic or obliterative infiltration of inflammatory cells. Histological studies in uveitis show peri vascular infiltrates of lymphocytes causing Peri vasculitis rather than true vasculitis of the vessel wall¹².

CD4+ T cells have been documented around & within retinal vessels suggesting a possible role of cell mediated immunity. In Behcet's disease, local endothelial injury & increased prothrombin activity causing thrombotic vascular changes are known¹³

The uniquely high retinal metabolism driven oxygen demand is met by its efficient vasculature. Hence, the retinal circulatory insufficiency causes rapid neuronal dysfunction & degeneration. As in this case, focal ischemia can cause rapid neuronal death of inner retinal layers resulting in irreversible visual loss. Retinal vascular obstruction can also promote abnormal production of Vascular endothelial growth factor causing increased vascular permeability and Macular edema as observed in this case, at an early stage

itself¹⁴. It also can cause Neo vascularization and related complications due to bleeding & fibrovascular proliferation.

Despite early diagnosis & institution of therapy with parenteral and oral anti virals & steroids, visual recovery was poor.

There are no prospective studies regarding the management & long term outcomes of Ischemic retinal vasculitis. In a retrospective study comparing 38 eyes(20pts) of Ischemic retinal vasculitis with 62 eyes(33pts), 34% in the ischemic group had final severe visual loss against 6% in the Non ischemic group¹⁵.

Management of retinal vascular inflammation is very challenging. Role of Immuno-suppressive or immune-modulatory drugs and the timing of the same in preventing retinal ischemia is hypothetical and poorly understood.

In the HAART era, AIDS related CMV retinitis has been successful in prevention of bilateral blindness, which was quite common earlier. This case of presumed viral retinitis with occlusive vasculitis relentlessly progressed to severe visual impairment. Also, diagnosis of INFECTIVE RETINITIS with OCCLUSIVE VASCULITIS was empirical as all tests were found negative. Only suggested etiology being non-specific immune suppression.

References:

1. Spector SA, McKinnley GL, Lalezari JP et al. Roche Cooperative Ganciclovir Study Group, Oral ganciclovir for the prevention of cytomegalovirus retinitis in persons with AIDS. *N Engl J Med* 1996;334:1491-1497
2. Shimakawa M, Kono C, Nagai T, Hori S, Tanabe K, Toma H. CMV retinitis after renal transplantation. *Transplant Proc* 2002;34:1790-1792
3. Jacobson MA, Stanley HH, Holtzer C, Margolis TP, Cunningham ET. Natural history and outcome of new AIDS-related cytomegalovirus retinitis diagnosed in the era of highly active antiretroviral therapy. *Clin Infect Dis* 2000;30:231-233
4. Lopez-Contreras J, Ris J, Domingo P, et al. Disseminated cytomegalovirus infection in an immunocompetent adult successfully treated with ganciclovir. *Scand J Infect Dis*. 1995;27:523-525
5. Jabs DA. Ocular manifestations of HIV infection. *Trans Am Ophthalmol Soc* 1995;93:623-683.
6. Gallant JE, Moore RD, Richman DD, Keruly J, Chaisson RE. Incidence and natural history of cytomegalovirus disease in patients with advanced human immunodeficiency virus disease treated with zidovudine. The Zidovudine Epidemiology Study Group. *J Infect Dis* 1992;166(6):1223-1227.
7. Jabs DA, Martin BK, Forman MS, Ricks MO, the Cytomegalovirus Retinitis and Viral Resistance Research Group. Cytomegalovirus (CMV) blood DNA load, CMV retinitis progression, and occurrence of resistant CMV in patients with CMV retinitis. *J Infect Dis* 2005;192(4):640-649.
8. Rao NA, Zhang J, Ishimoto S. Role of retinal vascular endothelial cells in development of CMV retinitis. *Trans Am Ophthalmol Soc* 1998;96:111-123. discussion 124-126.
9. Pepose JS, Holland GN, Nestor MS, Cochran AJ, Foos RY. Acquired immune deficiency syndrome. Pathogenic mechanisms of ocular disease. *Ophthalmology* 1985;92(4):472-484.
10. Thorne JE, Jabs DA, Kempen JH, Holbrook JT, Nichols C, Meinert CL, the Studies of Ocular Complications of AIDS Research Group. Causes of visual acuity loss among patients with AIDS and cytomegalovirus retinitis in the era of highly active antiretroviral therapy. *Ophthalmology* 2006;113(8):1441-1445.
11. A.M.AbuEl-Asrar, C.P.Herbert, and K.F.Tabbara, "Differential diagnosis of retinal vasculitis," *Middle East African Journal of Ophthalmology*, vol.16, no. 4, pp. 202-218, 2009.
12. J. D. Gass and C. L. Olson, "Sarcoidosis with optic nerve and retinal involvement," *Archives of Ophthalmology*, vol.94, no.6, pp.945-950, 1976.
13. E.H.Hughes and A.D.Dick, "The pathology and pathogenesis of retinal vasculitis," *Neuropathology and Applied Neurobiology*, vol.29, no.4, pp.325-340, 2003.
14. D.M.Rosenbaum, P.S.Rosenbaum, A.Gupta, M.D.Michaelson, D.H.Hall, and J.A.Kessler, "Retinal ischemia leads to apoptosis which is ameliorated by aurointricarboxylic acid," *Vision Research*, vol.37, no.24, pp.3445-3451, 1997.
15. H.E.Palmer, M.R.Stanford, M.D.Sanders, and E.M.Graham, "Visual outcome of patients with idiopathic ischaemic and nonischaemic retinal vasculitis," *Eye*, vol. 10, no. 3, pp. 343-348, 1996.