CMV retinitis in an immunocompetent 12years old

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Back ground : A case report of a 12year old immunocompetent male patient who developed CMV retinitis after having a shot of MMR vaccine.

Patient and Method : 12 year old male patient showed up with rapid progressive decrease in vison in the left eye , mild redness, ocular pain with photophobia that started 17days ago. A week earlier he visited another eye care unit and had a fundus photograph with multiple fluffy yellowish retinal infiltrates and Intraretinal hges in the posterior pole Fig 1. He received no treatment at that point.

He showed up at our facility 10 days later with BCVA - 1.0 in the right eye and unremarkable ocular exam . The left eye however had BCVA of 1/60 eye pressure of 10mmhg , AC cells rare with few fine kps in a deep AC with no PS . Fundus exam showed vitreous haze of 1+ with multiple fluffy yellowish areas of retinitis with intraretinal hges mainly along the infratemporal arcade , yet small multiple satellite retinitis could be seen all over the posterior pole. Disc oedema and macula oedema were detected . **Fig 2** - OCT scans of macula showing macular edema and thick retinitis of the inner retinal layers . Colored fundus photography and fluorescein angiography was performed for both eyes - **Fig 3**.

Fig 1: Colored fundus photograph one week after onset of his visual complaint showing multiple whitish fluffy retinal infiltrates in the posterior pole with Intraretinal hges

Review of system was unremarkable, except for administration of mumps – rubella - measles (MMR) vaccine 14days before onset of visual symptoms. There was no family history or personal history of immunodeficiency or unusual infections or autoimmune problems.

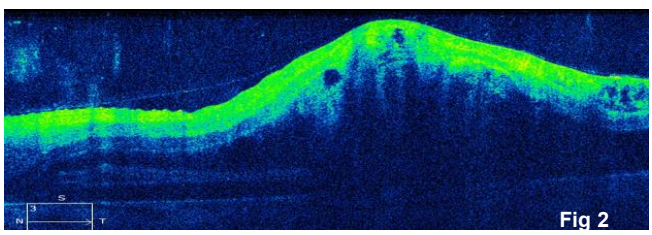
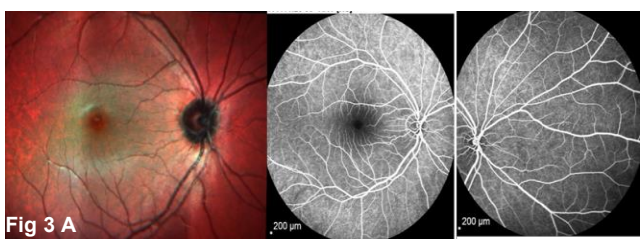
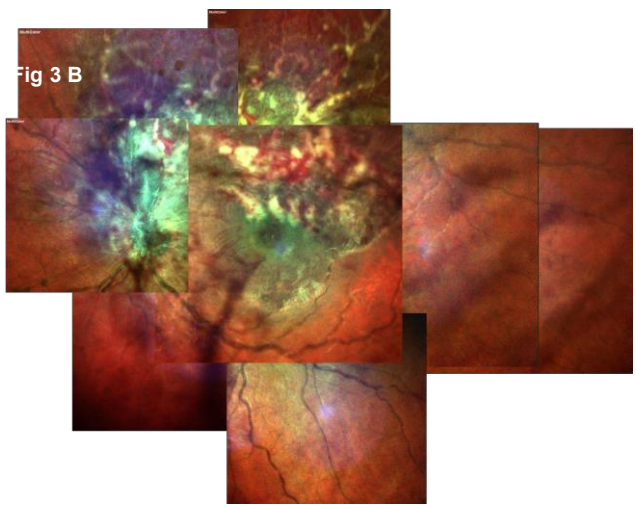


Fig 2 : Horizontal OCT scans through the macula showing macular oedema with hypereflective appearance of the inner macular layers corresponding to area of superficial retinal hge and retinitis





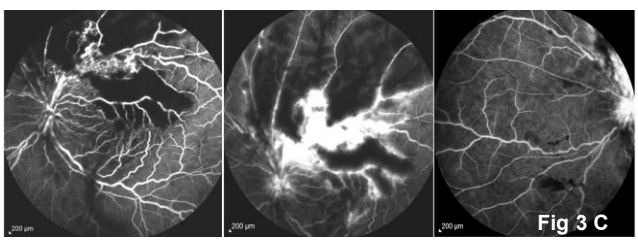


Fig 3 : A- colored images and fundus fluorescein angiogram showing normal findings of the right eye . B Colored image of the left eye showing extensive retinitis with Intraretinal hges mainly along the supratemporal arcade and involving the macula region B _ fundus images of the left eye showing severe ischeamia in the supratemporal retina and macula with late leakage along the aracade

Few differential were set in , including : infectious Acute retinal necrosis, CMV retinitis, Toxoplasmosis , HIV Syphilis and Behcet's been the non infectious differential . Other non infectious differentials including SLE , that may not be directly related but, thought to be a possible predisposing factor inducing opportunistic infection was considered.

The patient was worked up for all the above and a PCR sample from the anterior chamber to evaluate for viral panel and toxoplasma . In the same setting the patient was given intravitreal Ganciclovir 2mg/0.5ml , owing to the clinical appearance erring towards CMV retinitis.

Results: Labs came back with ,Syphilis IgG –negative , CMV –IgG positive , CMV IgM – equivocal, Toxoplasma Ig G and IgM negative CD 4T helper cell – were low 154cells/ul (350- 1391cells/ul), CD8 T cytotoxic cells – 179cells/ul (59- 699cells/ul),CD4/CD8 – 0.9, HIV 1 and 2 antibodies – negative , CBC showed Hemoglobin 10.3 , TLC 4.2 , Platelets 401 ALT -24 , AST- 25,Creatinine 0.6, urea- 27,FBS- 80 and Post prandial blood sugar – 99. ANA , DsDNA also returned unremarkable with a normal chest Xray . AC PCR came back positive for CMV .

At that point Valgancyclovir oral tablets were started along with solupred tablets 40mg and Ganciclovir intravitreal injection was continued. The patient had a total of 4 intravitreal injections

After the last intravitreal injection , only residual intraretinal hges were evident superiorly Fig 4 - However, oral Valgancyclovir was continued with monitoring of the CD 4 count and CBC.

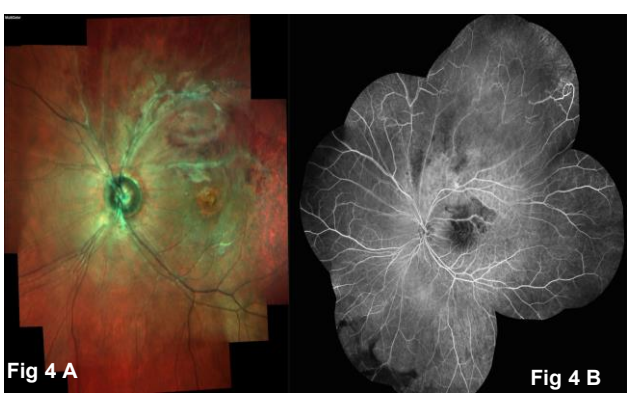


Fig 4 After the last intravitreal injection , residual intraretinal hges were evident superiorly A, with severe retinal ischemia evident on fundus fluorescein angiogram B.

Further work up was performed to investigate for secondary and primary immunodeficiency syndrome .

Preliminary tests for primary immunodeficiency included B cells (CD19, CD20), Natural killer cells (CD16, CD56) IgG, IgM, IgA, and IgE levels C3 level C4 level and CT chest to evaluate for thymus gland enlargement and abdominopelvic sonar , and all returned unremarkable. A bone marrow aspiration was discussed with the parents by the infection specialist but the parents refused.

CD 4 count was repeated with a gradual rise back to normal . CD 4- T helper cell was 154 cells/ul when the patient first showed up. After 21 days of Valganclyoivr it increased to – 257cells / ul and again 21 days later CD 4 - T helper cell – 506cells / ul. In the light of not been able to pin down a specific immunodeficiency disease the condition was considered idiopathic CD4 lymphoctopenia. (ICL) predisposing to CMV retinitis .

Vagancyclovir oral was continued for total of 3 months with monitoring of the renal functions and CBC. Steroids was tapered and discontinued with the antiviral therapy.

The patient had complete resolution of the retinitis and intraretinal hges , leaving an ischemic area in the superior macula and supratemporal retinal region. BCVA was 0.6 .

A month later, laser treatment was applied to the ischemic areas with laser rows applied beyond the ischemic retina . **Fig 5** shows ,colored images and OCT scans following laser by 2 months showing complete resolution of macular oedema and complete resolution of the retinitis with no recurrence off treatment with BCVA of 0.67 . By OCT scans the superior macula showed thinning of the inner layers denoting ischemia at previous site of retinitis . The patient was followed up for 1 year and showed no evidence of recurrence with stable vision.

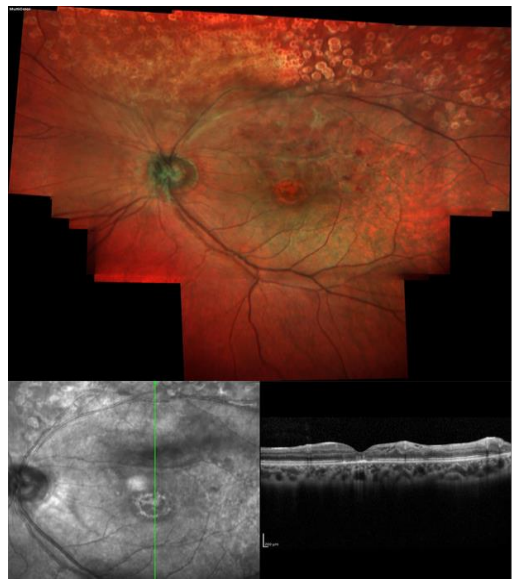


Fig 5 Colored fundus photo 2 months after laser treatment to the ischemic retina and B showing OCT scans through the macula with resolved macula oedema and thinning of the inner retina superiorly

Comment: CMV retinitis classically occurs in immunocompromised individuals including patients with HIV, systemic malignancies , patient on immunosuppressive drugs or after organ transplantation. It was also reported in 208 non HIV patients with predisposing factors including; 4.3 % with Good syndrome, 10.1 % related to intraocular or periocular corticosteroid administration, 33.1 % age over 60 years , 28.7% with malignancy 19.1 % a systemic autoimmune disorder requiring systemic immunosuppression , 15.2 % organ or 16.3 % bone marrow transplantation requiring systemic immunosuppression, and 6.1 % diabetes mellitus 4.5 % of the patients had no identifiable contributor to a decline in immune function (1) . It is important to note that 4.5% had no predisposing factors.

The reported patient here however, did not have any of the predisposing factors that can allow opportunistic infections and with an unexplained drop of the CD4 count and CD4/CD8 ratio so it was suggested to be idiopathic CD4 lymphoctopenia. (ICL).

Idiopathic CD4 lymphocytopenia (ICL) was defined by the United States Centers for Disease Control and Prevention (CDC) as a clinical condition in patients with depressed numbers of circulating CD4 T lymphocytes (<300 cells/µl or <20% of total T cells) at a minimum of two separate time points at least 6 weeks apart, with no laboratory evidence of infection with human HIV-1 or HIV-2, and the absence of any defined immunodeficiency or therapy associated with depressed levels of CD4 T cells (2).

The pathogenesis of ICL suggest a diminished generation of T cell precursors and a decreased clonogenic capacity of bone marrow progenitors, which may be due to a disturbed cytokine environment with, increased tumor necrosis factor-α (TNF-α) and decreased IL-2 levels (5).

The case reported here may closely correlate with the definition of ICL, or that he probably had developed another infectious condition that decreased the CD4 count and allowed CMV retinitis.

However it was important to consider the fact that this patient had an MMR vaccine shot before he developed the CMV retinitis.

Vaccine induced , transient T-cell depletion has been reported . It is well known that immunization with live virus vaccines may cause immunosuppression with lymphopaenia, impaired cytokine production and defective lymphocyte response to mitogenes . It was well described following measles vaccine (6-8), and studied in 2003 , focusing on rubella vaccine (9). The latter reports decrease in the CD3 and CD4 as early as 1 week following rubella vaccination of healthy individuals . The mechanism of this decline postulated to be transient lymphopaenia arising from virus-induced death of T cells (10)

Following rubella vaccine , particularly on day 7 , the CD3 and CD4 lymphocyte subsets significant decreased compared with the initial level .The IL-10 levels increased with from day 7 to a maximum on day 30 with simultaneous reduction in plasma IFNɣ and a profound decrease of peripheral blood lymphocyte with elevation of IL-4.

The provisional case definition by the CDC therefore also permits the inclusion of patients with panlymphocytopenia and normal CD4:CD8 ratio, although most of the published cases had a severely inverted CD4:CD8 ratio.

Transient CD4 lymphocytopenia, has been estimated to occur in 0.4–4.1% healthy HIV-negative individuals at any given time (3).

Unexplained CD4+ T-Lymphocyte Depletion in non HIV patients was reported in 1992 . 21 patients not known to be immunocompromised developed unusual opportunistic infections and showed transient CD 4 - T cells depletion. All patients had CD4 less than 300 with lymphoctopenia. They developed different opportunistic infection including Pneumocystis carinii pneumonia , Disseminated cutaneous herpes zoster, Disseminated molluscum contagiosum, (2).

Looking at it from another perspective common pathogenic bacterial, viral such as hepatitis B, Ebstein-Barr virus, cytomegalovirus, parasitic, and fungal diseases may depress CD4 cell counts, but usually without inversion of the CD4:CD8 ratio (4).

This changes proposed a cytokine ‘shift’ from type 1 cytokines early after vaccine inoculation to type 2 cytokines 1 month after vaccination is associated with activation of central mechanisms of immunosuppression (9).

This assumption is indirectly confirmed by changes in TNF-α /IL-10 ratios after rubella vaccine inoculation with a decrease in the TNF and an increase in the IL -10. The study concluded live attenuated rubella vaccine inoculation may cause sustained immunosuppression including defective lymphocyte response to mitogen and impaired cytokine production. The signs of immunosuppression may persist for at least 1 month after vaccination (9).

Conclusion: So the dilemma would remain if the patient actually suffered ICL that decreased the CD4 count and allowed CMV infection or was the CD 4 decline , infection or vaccine induced .inducing CMV retinitis . However, it is important to focus on the fact that CMV retinitis may develop in individuals not know to suffer from any form of immunodeficiency . In both situations the mode of treatment would be the same including intravitreal along with oral antivirals to resolve and decrease the incidence of recurrence .

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