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Do we need separate screening strategies for cytomegalovirus retinitis in different underlying immunosuppressed states? A retrospective study from Western India

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Purpose: The aim of this study was to describe the clinical features, course, and clinical outcomes of eyes with cytomegalovirus (CMV) retinitis in immunosuppressed patients of different etiologies. **Methods:** This was a retrospective observational study from a single ophthalmic tertiary care center. The patients included referrals from the nodal cancer center and the local human immunodeficiency virus (HIV) treatment clinic. Demographics, history, visual acuity, ocular features, treatment protocol, and final visual outcome of patients who were diagnosed with CMV retinitis in the period of five years from 2014 to 2019 were studied. **Results:** CMV retinitis was diagnosed in 25 eyes of 14 patients. Age of the patients ranged from 11–54 years. Ten (71.43%) patients were male and four (29.57%) were female. Eight of them had acute lymphoblastic leukemia (ALL), four were suffering from HIV infection and one patient each had lymphoma and history of a kidney transplant. The treatment for CMV retinitis ranged from two to sixty weeks depending on disease activity and systemic condition. Three of the patients were on maintenance therapy for ALL at the time of reactivation. **Conclusion:** Duration of treatment for CMV retinitis in patients of ALL was longer as compared to the other etiologies, and in recurrences, it needed to be continued till the completion of maintenance therapy for ALL. It is prudent to advise regular ophthalmic screening of all immunocompromised patients, as they are at a high risk of developing CMV retinitis. Patients of ALL, especially while on maintenance therapy, should be monitored for possible development or reactivation of CMV retinitis.

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Cytomegalovirus (CMV) belongs to the herpes class of viruses (HHV 5). It contains double-stranded DNA, causing lifelong latent infection.[1] Within the United States, seroprevalence is estimated to be 60% overall and rises with age, ranging from 36.3% in children aged six to eleven years to 90.8% in adults 80 years and older.[2] Systemic CMV infection in general population causes either no symptoms or just mild illness like fever, sore throat and fatigue. However, in immunocompromised patients it remains an important cause of opportunistic infection, with CMV retinitis being a definite risk to sight.

Clinically, there are three recognized ophthalmoscopic patterns of CMV retinitis: hemorrhagic, granular type or frosted branch angiitis (FBA). CMV retinitis is primarily a clinical diagnosis, based on the classic appearance of these lesions in susceptible individuals. For documentation of extension of CMV retinitis, the fundus is mapped into three zones depending on the area of retinal involvement. Zone 1 is the area within 3,000 µm from the fovea and 1,500 µm from the margin of the optic disc. Zone 2 is from Zone 1 to the vortex veins. Zone 3 is the remaining retina up to the ora serrata.[3]

CMV retinitis is primarily a disease of immunocompromised hosts. Individuals with acquired immunodeficiency syndrome (AIDS) from human immunodeficiency virus (HIV), malignancies, systemic immunosuppressive therapy, post-organ transplant, and primary immunodeficiency are at higher risk for developing CMV retinitis.[4] In patients of HIV infections, combination antiretroviral therapy (cART) has significantly reduced the occurrence of CMV retinitis among AIDS patients due to the improvement in blood counts. Despite that, CMV retinitis still remains the most common ocular opportunistic infection in patients with AIDS. Patients with a CD4+ T cell count <50 cells/microliter continue to be at increased risk of CMV retinitis, and screening in this population is essential.[4] Amongst patients with non-HIV causes of immunosuppression, ophthalmologists have been witnessing an increasing number of eyes developing CMV retinitis because of more widespread use of improved immunosuppressive therapy for auto-immune diseases, organ transplants, and malignancies.[5] We are a tertiary referral ophthalmic centre based in western India, routinely screening immunosuppressed patients from the nodal

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cancer centre as well as the local human immunodeficiency virus (HIV) treatment clinic in the vicinity. Due to limited literature on non-HIV CMV retinitis, we have been screening patients according to the well-established HIV protocols or on a case-to-case basis. Also, at present there are no studies from the Indian subcontinent comparing HIV and non-HIV presentation of CMV retinitis. The study aims to analyze the clinical features, treatment response and visual outcomes of patients of CMV retinitis with different etiologies seen in our retina clinic.

Methods

This was a retrospective observational study from a single tertiary eye care center. Patients diagnosed with CMV retinitis during a period of five years from 2014 to 2019 were studied.

The study was approved by the institutional ethics review board and adhered to the tenets of the Declaration of Helsinki.

The diagnosis of CMV retinitis was established by classical clinical presentation i.e., hemorrhagic, granular and FBA. The diagnosis was supported by clinical history, underlying systemic condition, and response to treatment. All patients, irrespective of age and underlying systemic illness and with a minimum of six months of follow up were included in the study.

Patients with preexisting retinal conditions like posterior uveitis of other etiologies, retinal vascular conditions, postocular trauma, post vitreoretinal surgeries, and those patients who were unable to follow up for six months were excluded from the study.

Patient demographics including medical history and treatment history were taken. Ocular examination including visual acuity (using ETDRS LogMAR chart) and slit-lamp biomicroscopic evaluation of anterior and posterior segment of the eye including the vitreous and posterior pole of the retina, using a +78 Diopter lens was done. Detailed dilated retinal evaluation with indirect ophthalmoscope using + 20 Diopter lens and scleral depressor was performed along with serial fundus photos at every visit. The outcome measures that were evaluated were treatment protocol, recurrences of CMV retinitis, complications, need for surgical intervention, and initial and final visual outcome.

Once diagnosed with CMV retinitis, intravenous ganciclovir was given in the dose of 5 mg/kg 12 hourly for 2-4 weeks depending upon the disease activity, followed by shift to oral valganciclovir. The dose of oral valganciclovir was 900 mg BD for initiation of therapy, followed by a maintenance dose of 450 mg BD, ranging from 1-15 months, based on resolution of the CMV lesions. Intravitreal ganciclovir was given in the dose of 2 mg/0.05 ml at 5 to 7 days interval for maximum up to 3 doses.

The location of CMV retinitis lesions largely dictated the treatment algorithm.[6] For patients with immediate sight-threatening lesions (zone 1), intravitreal injections in conjunction with systemic antiviral therapy were started. For patients in zone 2 or 3, systemic therapy alone with close observation was followed.[4] Oral valganciclovir was preferred for systemic therapy. Intravenous ganciclovir therapy was given when patient was admitted at the oncology centre for intravenous chemotherapy or when the cost of treatment was a burden.

Statistical tests were performed between HIV and non-HIV group. For age and change in visual acuity post-treatment, Mann – Whitney test was performed. For gender, laterality, complications and recurrences, Fisher's exact test was performed.

Results

Between the period of 2014 to 2019, 14 patients were diagnosed to have CMV retinitis at our centre. Demographics and underlying systemic illnesses are detailed in Table 1.

Twenty-five affected eyes of fourteen patients were included in the study. The mean presenting visual acuity of the affected eyes in logMAR was 0.83 +/- 0.89. The mean final visual acuity post treatment was 0.55 +/- 0.87 [Table 2].

Laterality, clinical presentation, zone of involvement, and treatment details are detailed in Table 3. The diagnosis of CMV retinitis was clinical. None of our patients were found to have vitritis or secondary vascular occlusions during the duration of their follow up. One eye had florid disc oedema at presentation [Fig. 1].

At the time of presentation, serum CMV DNA was available in five patients and it ranged from 2080 copies to 9850 copies/ml. Out of those five, three were patients of acute lymphoblastic leukemia (ALL) while two were HIV positive patients. Among the HIV positive cases, CD4 counts ranged from 3-18 cells/microlitre.

The course of treatment ranged from two weeks to 63 weeks depending on disease activity and systemic condition of the patient.

No patient was given a monotherapy of intravitreal Ganciclovir. Eleven patients (78%) received a combination of systemic and intravitreal ganciclovir therapy, seven (63.6%) were patients of ALL. Two of them had HIV and one was a kidney transplant patient. The disease activity responded well to ganciclovir and no other medication was needed in this series of patients.

During the course of treatment for CMV retinitis, one eye developed immune recovery uveitis (IRU) which responded well to topical steroids. CMV DNA levels in that patient at presentation was 9850 copies/ml. The eye with disc oedema resolved with antiviral treatment and eventually developed pale disc as sequel [Fig. 2]. Two eyes developed foveal atrophy and one eye each developed epiretinal membrane and cystoid macular edema as sequel of healed CMV retinitis.

One eye each of two patients developed rhegmatogenous retinal detachment (RD) with vitreous hemorrhage as complication of CMV retinitis. The first patient, who had HIV, underwent vitrectomy with silicone oil insertion. His vision stabilized to 20/60 after the surgery. The second patient who had ALL, showed a reattached retina on follow-up presentation while on antiviral therapy.

Table 1: Demographics and underlying systemic illnesses

1) Age:
Mean +/- SD - 27.7 years +/- 16.1 years
2) Sex:
Male - 10 (71.43%)
Female - 4 (28.57%)
3) Underlying systemic illness:
ALL - 8 (57.1%)
HIV - 4 (28.4%)
Lymphoma - 1 (7.1%)
Post renal transplant - 1 (7.1%)

Table 2: Visual outcomes, cause of immunosuppression, type of retinitis and treatment received of 14 patients with CMV Retinitis

Age/ Sex	Eye	Initial BCVA logMAR	Final BCVA logMAR	Zone	Cause of Immunosupression	Type of Retinitis	Route of Gancyclovir
43/M	OD	0.0	0.0	Z1	HIV	GRANULAR	I/Venous+Oral
	OS	0.2	0.2	Z1			
13/M	OD	1.9	0.3	Z1	T-ALL	GRANULAR	I/Venous+Oral
	OS	0.2	0.2	Z1			
14/F	OD	2.3	1.1	Z1	ALL	GRANULAR	I/Venous+I/Vitreal
	OS	0.0	0.0	Healed Retinitis			
12/F	OD	0.6	0.3	Z3	T-ALL	HAEMORRHAGIC	I/Venous+Oral+I/Vitreal
	OS	1.0	3.0	Z1			
30/M	OD	2.3	3.0	Z1	HIV	GRANULAR/FBA	Oral+I/Vitreal
	OS	0.5	0.5	WNL			
13/M	OD	2.3	0.2	Z1	ALL	GRANULAR	I/Venous+Oral+I/Vitreal
	OS	1.8	0.2	CMVR with RD			
52/M	OD	0.2	0.0	WNL	HIV	GRANULAR	Oral+I/Vitreal
	OS	0.3	0.5	CMVR with RD			
51/M	OD	1.9	-	Z1	H/O Kidney	GRANULAR/FBA	Oral+I/Vitreal
	OS	0.6	-	WNL	transplant		
54/M	OD	0.0	0.0	Z2	Lymphoma	HAEMORRHAGIC	I/Venous+Oral+I/Vitreal
	OS	0.2	0.5	Z1			
30/F	OD	2.0	2.0	Z1	ALL	HAEMORRHAGIC	I/Venous+I/Vitreal
	OS	0.2	0.2	Z1			
11/M	OD	0.6	0.3	Z1	ALL	HAEMORRHAGIC	I/Venous+I/Vitreal
	OS	0.6	0.3	Z1			
17/F	OD	0.0	0.0	Z3	ALL	HAEMORRHAGIC	I/Venous+I/Vitreal
	OS	1.9	0.0	Z1			
28/M	OD	0.5	0.5	Z1	ALL	FBA	I/Venous+I/Vitreal
	OS	0.0	0.0	Z1			
21/M	OD	0.0	0.3	Z1	HIV	HAEMORRHAGIC	Oral
	OS	0.0	0.0	Z1			

M: Male, F: Female, OD: Right Eye, OS: Left Eye, T-ALL: T cell Acute Lymphocytic Leukemia, HIV: Human Immunodeficiency Virus, FBA: Frosted Branch Angiitis, CMVR: Cytomegalovirus Retinitis, RD: Retinal Detachment, BCVA: Best Corrected Visual Acuity, Z1: Zone 1, Z2: Zone 2, Z3: Zone 3, WNL: Within normal limits, I/Venous: Intra venous, I/Vitreal: Intra Vitreal

Table 3: Laterality, clinical presentation, zone of involvement and treatment details

1) Laterality:
   Bilateral - 11 (78.5%)
   Unilateral - 3 (21.5%)
2) Clinical presentation:
   Haemorrhagic - 12 eyes (48%)
   Granular - 9 eyes (36%)
   FBA - 2 eyes (8%)
   Granular with FBA - 2 eyes (8%)
3) Zone of involvement:
   Zone 1-21 eyes (46.42%)
   Zone 2-2 eyes (7.14%)
   Zone 3-2 eyes (7.14%)
4) Systemic antiviral therapy:
   Intravenous ganciclovir only - 5 (35.7%)
   Oral valganciclovir only - 4 (28.5%)
   Intravenous ganciclovir followed by oral valganciclovir - 5 (35.7%)
5) Local antiviral therapy (intravitreal ganciclovir injection):
   Number of patients needing intravitreal injection - 11 (78%)
   Number of patients needing multiple intravitreal injections - 7 (50%)
   Number of eyes needing intravitreal injections - 15 (60%)
   Number of eyes needing multiple intravitreal injections - 10 (40%)

The mean duration of follow up for all patients was 17 months (range six months - 48 months). Three patients had bilateral reactivation after one to four months of having stopped CMV treatment, with hemorrhagic type of CMV retinitis in two patients and FBA in the third. Serum CMV DNA titers were available for two patients; the counts were 3580 copies/ml in the FBA presentation and 9830 copies/ml in the hemorrhagic retinitis presentation. All three were on maintenance chemotherapy for ALL at the time of reactivation. They were restarted on intravenous ganciclovir for 21 days. Two of those patients were also given two doses each of intravitreal ganciclovir. The lesions showed clinical resolution post intravitreal injections. In consultation with the oncologist, they were thereafter kept on maintenance therapy of ganciclovir 5 mg/kg/day till the remission of ALL.

There was no systemic adverse event/neutropenia from systemic antiviral treatment. CMV associated CNS infection was not noted in any of the patients. None of the patients succumbed to primary disease during maintenance phase of treatment or follow-up.

The subgroup analysis of the two major etiologies i.e., ALL and HIV is summarised in Table 4.

Visual acuity was worse in ALL group at presentation due to predominantly zone 1 involvement [Fig. 3]. Their final visual acuity was similar to non ALL group. This suggested that improvement in visual acuity was significantly better in ALL group.

Mean age for HIV group was 35 ± 12 years whereas mean age for non-HIV group was 22.8 +/- 14.9 years. This difference was statistically significant ($P = 0.026$). Gender difference between the two groups was statistically not significant ($P = 0.069$) as was laterality and complications between two groups. Comparing reactivation of CMV retinitis between ALL and non ALL group was not found to be conclusive because of small sample size.

Change in the visual acuity posttreatment was statistically significant between two groups (two-tailed $P = 0.029$). Non-HIV group had significantly more improvement in vision posttreatment as compared to the HIV group. This is attributable to the fact that non-HIV group had predominantly zone 1 involvement at presentation leading to poorer visual acuity at presentation.

Discussion

The most visually debilitating presentation of CMV retinitis is a slowly progressive necrotizing retinitis that may affect the posterior pole, the periphery or both, and it may be unilateral or bilateral. It is an end organ disease of immunosuppressed individuals with varied etiologies causing immunosuppression.[6]

In our study, CMV retinitis in patients of leukemia had clinically more widespread disease and had a worse prognosis than in HIV positive patients. It has been seen in published literature that presentation in non-HIV eyes is more aggressive, has an association with viral loads and needs prompt intervention.[6,7] The patients of ALL in our series were younger, had a bilateral presentation, and the eyes presented with hemorrhagic type of CMV retinitis. HIV positive patients presented with granular appearance of the fundus lesions with often unilateral involvement. CMV DNA was detected in all 5 patients that were tested, including 3 patients of ALL in whom CMV retinitis reactivated. Leukemic patients needed combination treatment for CMV retinitis; duration of treatment was longer, continued till the completion of maintenance therapy for leukemia. Lu *et al.* noted that

Table 4: Subgroup analysis of 2 major etiologies i.e., ALL and HIV

1) Age:
ALL - 6 (75%) Paediatric age group between 11-17 years
HIV - 4 (100%) above 21 years
2) Laterality:
ALL - 8 (100%) Bilateral
HIV - 2 (50%) Bilateral
3) Clinical presentation
ALL - 4 (50%) Haemorrhagic
3 (37.5%) Granular
1 (12.5%) FBA
HIV - 2 (50%) Granular
1 (25%) Granular with FBA
1 (25%) Haemorrhagic
4) Need for Intravitreal ganciclovir:
ALL - 7 (87.5%)
HIV - 2 (50%)

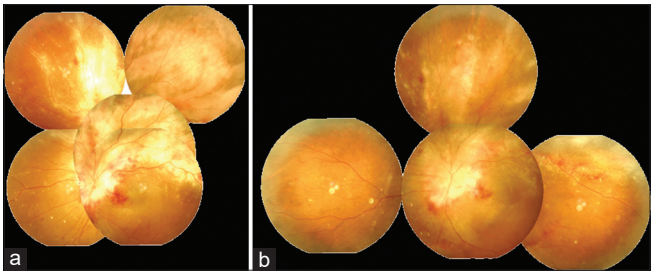

Figure 1: 17 years old female with history of ALL (a) Left eye fundus shows presence of white retinal infiltrates along the vessels with interspersed retinal haemorrhages and florid optic disc edema. (b) Left eye of the same patient showing resolving lesions post intravenous ganciclovir

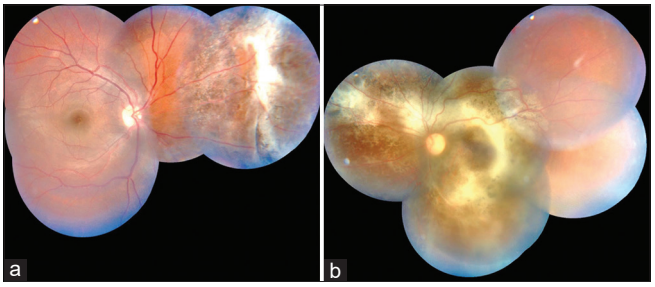

Figure 2: Sequelae of CMV retinitis in a 12 years old girl suffering from T cell Acute Lymphocytic Leukemia (ALL). (a) OD maintained good vision as the macula was spared with healed lesions in the periphery (b) OS denied PL with presence of healed scarred retinitis involving macula; also note the pale disc

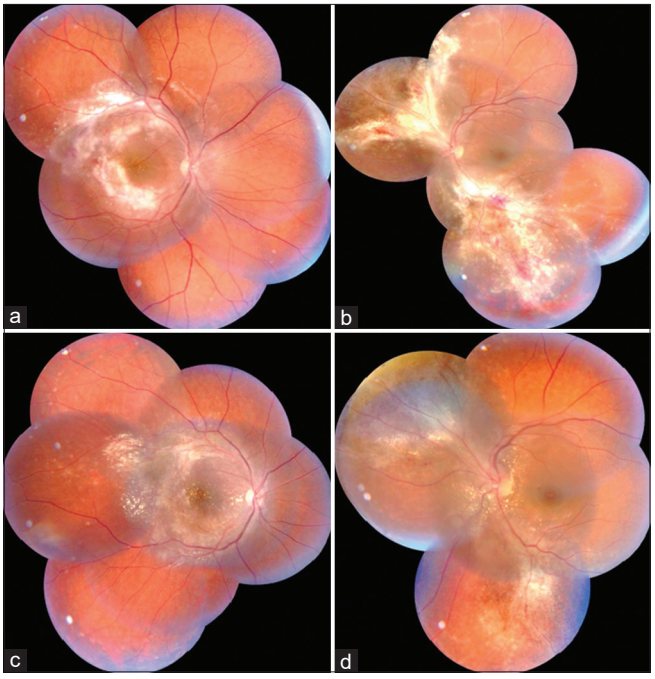

Figure 3: 13 years old boy with history of ALL. (a and b) Both eyes show active CMV retinitis with white infiltrates. (c and d) Same patient after 4 weeks of intravenous ganciclovir treatment with both eyes showing healed lesions

non-HIV immunocompromise-related retinitis had a more aggressive presentation with involvement of posterior retina and involved a greater area of the retina.[8] The findings in our study favour these results. In contrast, Kim *et al*. found that bilateral involvement and posterior involvement did not differ between the HIV and non-HIV groups. These mixed results in terms of degree and location of retinitis may be attributed to the level of immunosuppression.[9]

CMV Retinitis is usually a clinical diagnosis based on the typical fundus lesions. But in case of atypical presentations of CMV especially in non-HIV individuals simulating features of retinitis due to herpes simplex virus or varicella zoster virus, situations of clinical doubt might arise. Similarly, in patients with AIDS, other differentials such as acute retinal necrosis (ARN), HIV retinopathy, syphilitic retinopathy, progressive outer retinal necrosis (PORN), leukemic infiltrate and lymphoma should be kept in mind. In such situations, it is possible to confirm diagnosis of CMV with polymerase chain reaction (PCR) performed on aqueous or vitreous sample.[10,11] In our group of patients, as the clinical picture was quite definitive and the patients responded to treatment, we did not need to send an ocular sample for PCR.

There is good literature support available for treatment protocols for CMV retinitis in HIV positive patients in the post-HAART era, whereas less so for non-HIV patients. In non-HIV and HIV patients on anti-CMV drug treatment, resolution of the retinal opacity with resultant atrophy is considered a reliable sign of CMV inactivity, which was also seen in our group of patients. Treatment of CMV retinitis in non-HIV patients needs to be started in conjunction with their oncologists and physicians due to the existing immunosuppression and potential risk of further myelosuppression by the systemic antiviral.[6,12] Studies have also been advocating repeat intravitreal injections of ganciclovir in these patients to reduce the systemic toxicity on the patients.[5] Non-HIV immunosuppressed patients continue to have low blood counts as a nature of their ongoing treatment, which might lead to an activation of latent CMV.[13] Close consultations with the physician is important to monitor blood CMV levels, blood counts and CMV retinitis activity with regards to the treatment. The systemic therapy administered to our patients was guided by their oncologists and physicians. There has been significant work in recent times on monitoring leukemic patients with their blood counts and CMV DNA titres.[7,13]

In our series, oral valganciclovir was preferred for systemic therapy. Intravenous ganciclovir therapy was given when patient was admitted at the oncology center for intravenous chemotherapy or when the cost of treatment was a burden. Intravitreal Ganciclovir was used in case of macula threatening lesions in conjunction with systemic therapy, with good results.

In our case series, one HIV and one ALL patient developed CMV retinitis associated retinal detachment (RD). The incidence of RD has not been found to significantly differ comparing HIV and non-HIV CMV retinitis patients, except in one small case series where HIV patients had higher rates of RD and more clock hours of retinitis on presentation than non-HIV patients.[14] One patient from our series needed surgical intervention in the form of vitrectomy with silicone oil tamponade, and his vision stabilized to 20/60 after the intervention. RDs in CMV retinitis are typically rhegmatogenous and arise from multiple breaks within the necrotic retina. Risk factors include larger areas of retinitis, bilateral disease, and active retinitis near the vitreous base. Surgical management of rhegmatogenous RD in eyes with CMV retinitis is challenging. Despite it being challenging, anatomical outcomes post-surgery are favourable for the vast majority of patients (78%) with favourable visual outcomes in a majority (56%).[15-17]

Risk factors for IRU include immune reconstitution with ART, more extensive CMV lesions and the use of Cidofovir.[18] One case from our series developed IRU, who was successfully treated with intensive topical steroids. The serum CMV DNA in this patient was found to be elevated at 9850 copies/ml. We therefore need to watch for IRU during followup, also for differentiating between IRU and CMV infection.[19]

In our series, three eyes had recurrences of CMV retinitis. All three recurrences were seen in patients on maintenance chemotherapy for ALL (35.5% of ALL patients). Two patients had elevated serum CMV DNA titers at the time of recurrence. We postulate that premature stoppage of antiviral treatment especially in the setting of persisting leucopenia in pharmacologically immunosuppressed patients could be the reason of reactivation in these patients as compared to HIV associated CMV retinitis, where the blood counts improve on commencement of HAART therapy. A significant study in patients of non-transplant pediatric ALL patients on chemotherapy revealed a high CMV DNAemia and low leucocyte counts in the maintenance phase of the chemotherapy. The authors postulated that a low leucocyte count was associated with high CMV DNAemia.[13] Jain *et al.* postulated a loss of cell-mediated immunity with delayed reconstitution during maintenance phase of chemotherapy for ALL.[7] Lu *et al.* followed 20 non-HIV immunosuppressed patients for 17 months and found a recurrence rate of 33.3% following discontinuation of anti-CMV therapy.[8] Kuo *et al*. found that after immunosuppressive therapy was discontinued in non-HIV immunosuppressed patients, 56% were able to discontinue anti-CMV therapy and had no subsequent CMV retinitis reactivation.[9] Our patients of reactivated CMV retinitis, having been kept on maintenance therapy of intravenous ganciclovir 5 mg/kg/day till the remission of ALL, along with a close monitoring of absolute leucocyte count and serum CMV DNA by the oncologists, had a good outcome. This finding emphasized the need for stringent monitoring of blood counts and longer duration of CMV treatment in immunosuppressed patients especially those with leukaemia on maintenance therapy.

CMV retinitis is slowly progressive. Patients, especially children, might remain asymptomatic till encroachment into the macula. Physicians and oncologists have acknowledged the reactivation of latent CMV infections with immunosuppression leading to CMV end organ disease including CMV retinitis, and the need for screening by measuring blood counts, CMV DNA levels and ophthalmic screening[13] but formal protocols as seen with patients of HIV with CMV viremia are yet to be established for non-HIV patients.

The course and mode of treatment for CMV retinitis needs a patient based approach depending on disease activity and the patient's systemic condition. In our series, even though test to compare recurrences between ALL and non ALL group was inconclusive due to small sample size, direct comparison suggested that ALL patients on maintenance stage of chemotherapy have a higher risk of recurrence of the infection. To the best of our knowledge, we are also the first to observe that this reactivation has an aggressive presentation. Therefore we advise an early intervention and prolonged

course of antiviral treatment in these patients, as suggested by Celiker H *et al*.[12]

Our study has the following limitations. It was a retrospective study with a small sample size. We therefore recommend a larger study involving multiple centres, including measures of CMV DNA levels which will enable to form guidelines for screening in immunocompromised patients especially other than HIV associated CMV retinitis.

Conclusion

Our study represents significant real-world data from the Indian subcontinent comparing CMV retinitis and its presentation in HIV and non-HIV patients. Based on our findings, we therefore advise that patients with CMV retinitis should undergo close follow up with retinal evaluation for the status of activity. It should also continue posttreatment for CMV retinitis, to keep a check on possible reactivation. It is also important to have regular consultation with the physicians specifically regarding the patient immune status in HIV and especially non-HIV patients, and tailor the follow-up based on patient's immune status and duration of immunosuppression.

We also suggest that immunocompromised patients who have a high risk of developing CMV retinitis should undergo detailed ophthalmic evaluations including retinal screening at regular intervals. This will ensure early diagnosis and prompt treatment.

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Conflicts of interest

There are no conflicts of interest.

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