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SHORT COMMUNICATION

Cytomegalovirus retinitis in a patient with non-Hodgkin's lymphoma: A diagnostic dilemma

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PURPOSE. *Patients with lymphoma can rarely develop cytomegalovirus (CMV) retinitis. Clinically it is difficult to distinguish from intraocular lymphoma. Also, in such cases the CD4+ count may be high. The authors report a rare case of bilateral CMV retinitis in a patient with non-Hodgkin's lymphoma with high CD4+ counts.*
METHODS. *Observational case report with review of literature.*
RESULTS. *CMV retinitis was clinically suspected due to the presence of large areas of retinal necrosis and hemorrhages in one eye and a demarcation line with white mottled retina in the other eye. Other differential diagnoses considered were intraocular lymphomatous infiltration and acute retinal necrosis due to herpes group of viruses. The diagnosis of CMV retinitis was confirmed by polymerase chain reaction performed on vitreous sample.*
CONCLUSIONS. *CMV retinitis can develop in cases of lymphoma despite high CD4+ counts. An early diagnosis can be established by performing PCR on vitreous biopsy. (Eur J Ophthalmol 2005; 15: 153-7)*

KEY WORDS. *Cytomegalovirus retinitis, Non-Hodgkin's lymphoma, Polymerase chain reaction, CD4+ count, Vitreous biopsy*

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INTRODUCTION

Classically, cytomegalovirus (CMV) retinitis occurs in HIV-infected individuals with a CD4+ cell count less than 50/µL (1). It has also been described in immunocompromised patients such as patients with organ transplantation or lymphoma (2, 3). In cases of lymphoma it presents a diagnostic challenge as its clinical picture may mimic that of intraocular lymphomatous infiltration. Also, in such cases the CD4+ count may be high (3). We report a rare case of bilateral CMV retinitis in a patient with non-Hodgkin's lymphoma with high CD4+ counts.

Case report

A 40-year-old man presented with sudden onset of painless diminution of vision in the right eye of 2 weeks' duration. He had non-Hodgkin's lymphoma treated earlier with cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP regimen) that currently was in remission for the past 3 months. On examination he had no perception of light in the right eye and 6/12 in left eye with accurate light projection. Slit lamp biomicroscopy of the right eye revealed signs of anterior uveitis in the form of 2+ cells in anterior chamber and fresh fine keratic precipitates. There was no sig-

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nificant reaction in the vitreous. On fundus examination there were large areas of retinal whitening and hemorrhages extending from the disc to the periphery (Fig. 1). In the left eye there was no anterior uveitis or vitritis. The disc and posterior pole were within normal limits but inferotemporal peripheral retina showed a whitish demarcation line between affected and normal retina. The affected retina had a white mottled appearance (Fig. 2).

Fundus fluorescein angiography revealed disc leak and diffuse choroidal leak with no significant vasculitis in the right eye. In the left eye there was granular hyperfluorescence due to pigment epithelium atrophy.

After 3 weeks the vision remained the same in both eyes. In the right eye the hemorrhages started resolving with disc pallor and necrotic retina becoming more evident whereas in the left eye the picture remained the same.

There was a history of chicken pox 2 months previously and the patient at present had postherpetic neuralgia involving the face. Investigations revealed hemoglobin of 10 g%, TLC 6800/mm^3, DLC-N 48, L 42, E 2, M 8, erythrocyte sedimentation rate 27 mm FHR, enzyme-linked immunosorbent assay for HIV was negative, CD4+ count was 979/µL (61.25%), and CD8+ was 192/µL (12%). A vitreous biopsy of the right eye was done and sent for cytology and polymerase chain reaction (PCR) for CMV and herpes simplex virus. No malignant cells were found in the vitreous biopsy. PCR for CMV performed on the vitreous sample was positive. A retinal biopsy could not be done as the patient did not give consent for the procedure.

As the right eye was already PL negative and the lesions in the left eye were static, no treatment was started and the patient was asked to follow-up regularly. At 3-month follow-up the fundus features remained the same.

TABLE I - SUMMARY OF CASES OF CYTOMEGALOVIRUS (CMV) RETINITIS IN LYMPHOMA PATIENTS

Case No.	Clinical picture	Systemic disease
1	Postmorte m diagnosis	Hodgkin's lymphoma
2	White retinal area with hemorrhage (unilateral)	Hodgkin's lymphoma
3	Sheathing with white retinal lesion with hemorrhage (unilateral)	Non-Hodgkin's lymphoma
4	Sheathing with white retinal lesion with hemorrhage (unilateral)	Hodgkin's lymphoma
5	Vasculitis with white retinal lesion with hemorrhage, lipid exudation and serous macular detachment (unilateral)	Hodgkin's lymphoma
6	Perivascular patch, retinochoroidal yellow-white discoloration with hemorrhages (unilateral)	Non-Hodgkin's lymphoma
7	Sheathing with white retinal lesion with hemorrhage (unilateral)	Angioimmunoblastic T-cell lymphoma
8	Vasculitis with vitritis with peripheral retinitis (bilateral)	Non-Hodgkin's lymphoma
9*	White retinal area with hemorrhage with necrosis in right eye, other eye peripheral granular demarcated retina	Non-Hodgkin's lymphoma

*Our case. PCR = Polymerase chain reaction

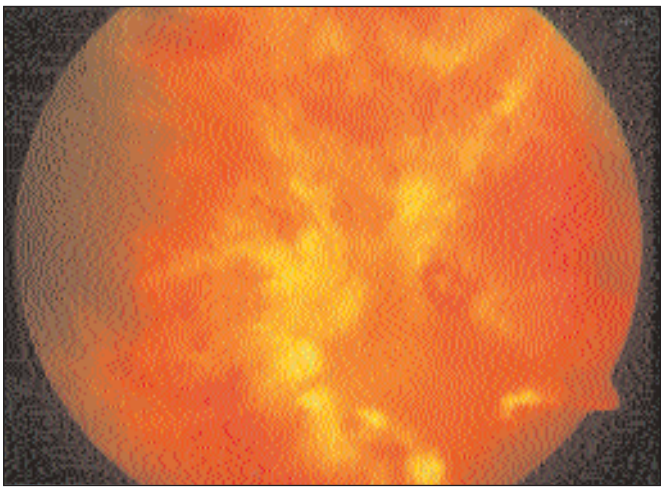

Fig. 1 - *Fundus photograph of the right eye showing large areas of retinal whitening and hemorrhages extending from the disc to the periphery.*

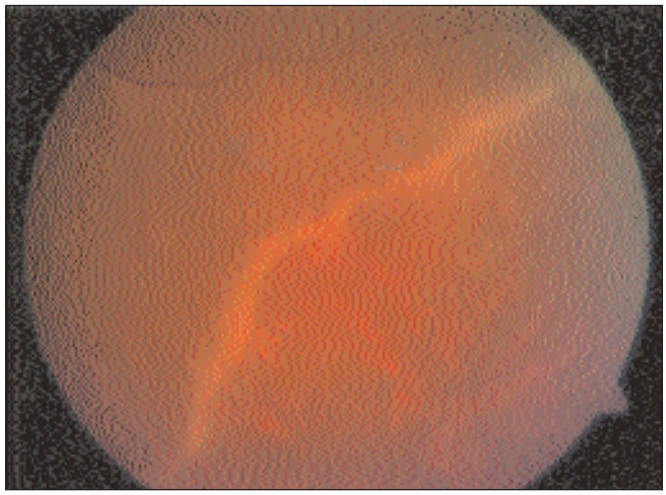

Fig. 2 - *Fundus photograph of the inferotemporal peripheral retina of the left eye showing a whitish demarcation line between affected and normal retina. The affected retina has a white mottled appearance.*

continued

Case No.	Diagnostic investigation	CD4+ count	Treatment	Outc ome
1	Inclusion body at postmortem	—	—	Died
2	Inclusion body at postmortem	Total lymphocyte count-300/µL	—	Died
3	CMV in urine and throat, rising titers	—	Adenosine arabinoside	Stable (2 years)
4	CMV in urine	—	Acyclovir	Died
5	PCR from vitreous count-620/µL	Total lymphocyte and foscarnet	Ganciclovir (3 years)	Stable
6	DNAemia and CMV isolatio n from vitreous	—	Ganciclovir and intraocular ganciclovir	Resistant, other eye also involved, died
7	DNAemia and antigenemia	212/µL ganciclovir	Ganciclovir and intraocular	Stable (17 months)
8	PCR positivity of vitreous sample	Total leukocyte count-9,600/µL	Ganciclovir, vitrectomy with silicone oil injection	Stable (1 month)
9	PCR positivity of vitreous sample	979/µL	—	Left eye stable (2 months)

DISCUSSION

CMV is a double-stranded DNA virus belonging to the *Herpetoviridae* family and an obligatory intracellular organism. Most individuals are exposed to the virus in childhood/early adulthood but innate immune response mechanism restricts the early stages of infection and delays spread of virus. The incidence of exposure increases with age. Infection usually remains latent. Defense mechanisms include interferon and NK cells. Antibody restricts the spread of virus to neighboring cells and tissue by neutralizing virus infectivity. CD4+ and CD8+ cells play an important role in virus infection/reactivation.

In adults the clinical disease most likely results from reactivation of latent infection, but may also occur with newly acquired infection. CMV is a rare cause of disease, except in patients with severe immunosuppression because of either HIV/AIDS or pharmacologic immunosuppression for organ transplantation, autoimmune disease, or malignancy. In AIDS, CMV retinitis is a presenting feature in 2% of cases and occurs in 20 to 30% of cases (4). In contrast, CMV retinitis is rare in malignant lymphoma despite the fact that 13.6 to 74% of patients with malignant lymphoma have CMV infection diagnosed at autopsy (5). On a MEDLINE search we found only eight cases of CMV retinitis reported in cases of lymphoma in the English literature (3, 6-12). These cases have been summarized in Table I. Out of the nine cases (including ours), four had Hodgkin's lymphoma and five had non-Hodgkin's lymphoma. Most of the cases were unilateral, one being bilateral symmetric, while our case had a bilateral asymmetric presentation. In most of the cases the clinical picture consisted of areas of retinal whitening with hemorrhages and vasculitis. Significant vitreous reaction was present in one case only. Four cases treated with ganciclovir have been reported as being stable while one case was resistant to ganciclovir and another required additional vitrectomy with silicone oil injection. CD4+ counts are not available in all the cases but in those mentioned the count was not <50/µL.

There is positive correlation between CMV retinitis and CD4 lymphocytes count. Retinitis most commonly occurs when the CD4 cells are <50/µL (1). Unlike in HIV/AIDS, CMV retinitis in post organ transplant or in patients with malignancy treated with chemotherapy can occur with normal CD4+ cell count (2, 3). However, in only one of the previously reported cases of CMV retinitis in lymphoma patients was there documentation of CD4+ count (Tab. I). It has been postulated that of the CD4+ cells the memory subset (CD4+ CD45RO+) cells play a more important role than the naive subset (CD4+ CD45RA+) cells in prevention of CMV retinitis and lymphoma/chemotherapy more severely affects the memory subset CD4+ cells (13). We cannot say whether lymphoma patients are more prone to develop CMV retinitis or the immunosuppression due to chemotherapeutic agents makes them more susceptible to this disease.

In our patient the initial differential diagnosis considered was intraocular lymphomatous infiltration, CMV retinitis, or acute retinal necrosis due to herpes group of viruses. Intraocular infiltration in patients with non-Hodgkin's lymphoma can present as a focal retinitis along retinal vessels, which can progress to involve a large part of the retina, choroiditis, chorioretinitis, and sub-retinal pigment epithelium infiltrates (14). This would also appear as an area of retinal whitening with associated hemorrhages. The history of recent chicken pox made us consider the possibility of herpetic retinal necrosis. However, the absence of severe vitritis and vasculitis in our patient did not favor a diagnosis of acute retinal necrosis. A similar patient with lymphoma and bilateral retinal necrosis with history of chicken pox diagnosed with CMV retinal necrosis has been reported (12). Thus two infective agents might simultaneously exist in an immunocompromised patient causing different disease processes.

The diagnosis of CMV was established in our case by PCR positivity of the vitreous sample. The sensitivity and specificity of PCR of vitreous sample to diagnose CMV retinitis is reported to be very high (92.3% and 98%, respectively) (1). Retinal biopsy is considered the hallmark for diagnosing or refuting lymphoma. However, our patient did not give consent for the procedure. The absence of malignant cells in the vitreous sample and the patient being in remission strongly suggest that our case was not of intraocular lymphoma.

We did not institute any treatment in our patient as the right eye did not have any perception of light and the lesions in the left eye were stable and self limited. This could be due to the changing immune status of lymphoma patients, unlike cases of AIDS. We

now have a 3-month follow-up of the case, over which time the left eye lesions have remained stable. This could be because the patient is presently in remission.

In conclusion, it is important to consider CMV retinitis as a differential diagnosis in all immunocompromised patients irrespective of their CD4+ counts. The most common presentation is perivascular areas of retinal whitening, hemorrhages, and vasculitis with associated mild uveitis. PCR of vitreous biopsy is a minimally invasive investigation that can provide an early diagnosis, which is important in this potentially treatable condition.

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