A possible coincidence of cytomegalovirus retinitis and intraocular lymphoma in a patient with systemic non-Hodgkin’s lymphoma

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Abstract

Purpose: To present a possible coincidence of cytomegalovirus retinitis and intraocular lymphoma in a patient with systemic non-Hodgkin’s lymphoma.

Case presentation: A 47-year-old woman presented with decreased visual acuity associated with white retinal lesions in both eyes. A history of pneumonia of unknown aetiology closely preceded the deterioration of vision. Five years previously the patient was diagnosed with follicular non-Hodgkin’s lymphoma. She was treated with a chemotherapy regimen comprised of cyclophosphamide, adriamycin, vincristin, and prednisone with later addition of the anti-CD20 antibody rituximab. She experienced a relapse 19 months later with involvement of the retroperitoneal lymph nodes, and commenced treatment with rituximab and 90Y-ibritumomab tiuxetan. A second relapse occurred 22 months after radioimmunotherapy and was treated with a combination of fludarabine, cyclophosphamide, and mitoxantrone followed by rituximab. The patient experienced no further relapses until the current presentation (April, 2010).

Pars plana vitrectomy with vitreous fluid analysis was performed in the right eye. PCR testing confirmed the presence of cytomegalovirus in the vitreous. Atypical lymphoid elements, highly suspicious of malignancy were also found on cytologic examination. Intravenous foscarnet was administered continually for three weeks, followed by oral valganciclovir given in a dose of 900 mg twice per day. In addition, the rituximab therapy continued at three monthly intervals. Nevertheless, cessation of foscarnet therapy was followed by a recurrence of retinitis on three separate occasions during a 3-month period instigating its reinduction to the treatment regime after each recurrence.

Conclusions: Cytomegalovirus retinitis is an opportunistic infection found in AIDS patients as well as in bone marrow and solid organ transplant recipients being treated with systemic immunosuppressive drugs. This case presents a less common incidence of cytomegalovirus retinitis occurring in a patient with non-Hodgkin’s lymphoma. We demonstrated a possible coexistence of cytomegalovirus retinitis and intraocular lymphoma in this particular patient. The final diagnosis was based on clinical manifestations together with the course of uveitis and its response to treatment alongside the results of vitreous fluid analysis. This report highlights the importance of intraocular fluid examination in cases with nonspecific clinical manifestations. Such an examination allows for the detection of simultaneously ongoing ocular diseases of differing aetiologies and enables the prompt initiation of effective treatment.

Keywords: Cytomegalovirus, Cytomegalovirus retinitis, Foscarnet, Non-Hodgkin's lymphoma, Rituximab, Valganciclovir

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Background
Cyto­me­gal­o­virus (CMV) re­ni­tis is a se­ver­e sight­threat­en­ing dis­ease which pre­va­lently af­fects pa­tients with AIDS [1-3]. CMV re­ni­tis may also oc­cur in pa­tients who are lymphopenic se­cond­ary to im­mu­nosup­pres­sive ther­apy after bone mar­row or solid organ trans­plant­a­tion [4,5]. Un­less ef­fective treat­ment is prompt­ly ini­ti­ated, the dis­ease may lead to pro­gres­sive vi­sual loss and blind­ness [6,7].

Gen­er­al­ly, im­mu­ne re­cov­ery uve­i­tis (IRU) should be con­sidered in the dif­fer­en­tial di­ag­no­sis of CMV re­ni­tis. IRU is an in­traoc­ular in­flam­ma­tory dis­or­der ori­gin­ally de­scribed in in­divi­duals with hu­man im­mu­nodef­iciency virus (HIV) and in­ac­tive cy­to­me­gal­o­virus re­ni­tis fol­low­ing highly ac­tive an­ti­re­tro­vi­ral ther­apy. IRU also oc­curs in iatrogene­ni­cally im­mu­nosup­pres­sive in­divid­uals in the con­text of taper­ing im­mu­nosup­pres­sive treat­ment [8].

This re­port fo­cuses on a less com­mon case of cy­to­me­gal­o­virus re­ni­tis oc­cur­ring in a pa­tient with sys­temic non-Hodg­kin’s lymph­oma. It pre­sent­s an in­ci­dence of sim­ul­tan­eous oc­cur­rence of cy­to­me­gal­o­virus re­ni­tis and in­traoca­lar man­i­fest­a­tion of non-Hodg­kin’s lymph­oma.

Case pre­sen­ta­tion
A 47-year-old woman pre­sented with de­creased vi­sual acu­ity as­so­ci­ated with white re­tinal le­sions in both eyes. A his­tory of pneu­monia of un­known aeti­o­logy clos­ely pre­ceded the de­terior­a­tion of vi­sion. Five years pre­vi­ously the pa­tient was di­ag­nosed with fol­li­cu­lar non-Hodg­kin’s lymph­oma (De­c­em­ber, 2004). She un­der­went eight cy­cles of com­bi­na­tion che­mo­ther­apy that in­clud­ed cyclo­pho­sa­mide, adria­myc­in, vin­cri­stine and pre­nis­one with lat­er ad­di­tion of the an­ti-CD20 an­to­body ritux­im­ab. The pa­tient was in re­mis­sion for 19 months. Fol­low­ing a re­lap­se with in­volvement of the retroperito­neal lymph nodes (Fe­bru­ary, 2007), ritux­im­ab and 90Y-ibritu­mon­ab tiu­xetan were ad­min­is­tered. A sec­ond re­lap­se oc­curred 22 months post ra­dio­i­mmu­no­ther­apy (April, 2009). Four com­bi­na­tion cy­cles of flud­a­ra­bine, cyclo­pho­sa­mide, and mito­xan­tron­e were then un­der­taken lead­ing to par­tial re­mis­sion. Sub­se­quent ther­apy in­clud­ed ritux­im­ab ad­min­is­tered once per month for four months and once every third month there­after. No fur­ther re­lap­ses were ex­pe­ri­enced from April, 2009 to April, 2010.

At pre­sen­ta­tion (April, 2010), her best-cor­rected Snell­en vi­sual acu­ity (BCVA) was 6/12 in the right eye and 6/9 in the left eye. There were large ker­atic precip­i­ta­tions and a mil­d an­ter­i­or cham­ber ce­re­bral re­ac­tion pre­sent in both eyes (Fig­ure 1). Ex­am­i­na­tion of the fundus re­vealed bil­a­teral find­ings of mod­erate vi­tre­ous opa­ci­ties, pale optic discs, re­ti­nal nec­ro­sis with re­ti­nal in­fil­tra­tions, sev­eral hem­or­rhages in the pos­ter­i­or pole and ar­eas of peri­ph­er­i­al re­tinal atrophy. Some ves­sels dis­played ex­tensive white she­ath­ing pro­vid­ing them with the ap­pear­ance of frosted branch an­gi­i­tis (Fig­ure 2). De­spite prophyl­a­ctic an­ti­vi­ral ther­apy (valganc­lo­vir 900 mg twice per day and valac­lo­vir 500 mg once per day) and main­ten­ance treat­ment with ritux­im­ab (800 mg once per three months), the most like­ly di­ag­no­ses were CMV re­ni­tis or in­traoca­lar non-Hodg­kin’s lymph­oma. Blood tests re­vealed neu­tro­penia (0.9 × 10⁹/L) with a nor­mal lympho­cyte count of 1.2 × 10⁹/L. Ser­ology was neg­a­tive for HIV.

Pars plana vit­rec­to­my was per­formed in the right eye for both di­ag­no­stic as well as ther­apeu­tic pur­poses (June, 2010). Vit­re­ous fluid an­a­lysis con­firmed CMV by means of PCR test­ing. Fur­ther­more, cy­tol­o­gic ex­am­i­na­tion re­vealed atypical lymp­ho­cytes with lob­u­lated nuclei and basophi­lic cyto­plas­ma (Fig­ure 3) on a back­ground of lyt­ic cells. Two special­ists con­firmed the find­ing of highly sus­pi­cious ma­lignant ele­ments in the vit­re­ous fluid. Treat­ment with in­tra­ve­tr­i­al foscar­net was given con­tin­u­ously for three weeks fol­lowed by oral valganc­lo­vir given in a dose of 900 mg twice per day. Ritux­im­ab ther­apy was also main­tained and ad­min­is­tered ev­ery three months. The di­ag­no­sis of in­traoca­lar lymph­oma is usu­ally an in­di­ca­tion for in­tra­ve­tr­i­al treat­ment with meth­otrex­ate in ad­di­tion to sys­temic ther­apy. In­tra­ve­tr­i­al meth­otrex­ate ther­apy was not con­sid­ered in this case as
PCR testing confirmed infectious uveitis of cytomegalovirus aetiology. In such infectious cases, methotrexate could probably worsen the course of ocular disease.

Retinal findings responded well to treatment and retinitis regressed. However, BCVA decreased to 6/24 in the right eye and 6/12 in the left eye, perimetry revealed scotomas (Figure 4) and moderate vitreous haze persisted in the left eye (Figure 5). The main cause of visual impairment was most likely pallor of the optic disc.

A relapse of retinitis in the three weeks following discontinuation of foscarnet treatment necessitated its reinduction and administration once again continually for three weeks (August, 2010). BCVA reduced to hand movements in the right eye and 6/18 in the left eye and further progression of visual field defects was demonstrated (Figure 6). A further recurrence developed within one week of cessation of this therapy. Consequently, the patient was retreated with foscarnet administered as a bolus three times per week (September, 2010). This therapeutic regime proved to be insufficient as retinal lesions once again showed signs of reactivation. Moreover, an increase in plasmatic CMV DNA copies was detected (Figure 7). The patient was admitted to a hematologic clinic and treatment with intravenous foscarnet was administered continually for further three weeks (October, 2010). Systemic examination for restaging of the follicular lymphoma was also undertaken. An MRI of the brain showed no signs of lymphoma. Cerebrospinal fluid was negative for CMV. No pathological changes were revealed by immunophenotyping and cytologic examination of cerebrospinal fluid.

Retinal lesions were in regression, but plasma CMV DNA copies were still positive giving rise to consideration of cidofovir therapy. The patient declined this treatment. Maintenance therapy with rituximab was also discontinued.

Two months after the most recent foscarnet therapy (December, 2010), negativity of CMV DNA copies in the plasma was detected. However, BCVA had decreased to hand movements in the right eye and 1/60 in the left eye.
Figure 4 Results of perimetry. A, right eye. B, left eye. Large visual fields defects.
due to a combination of optic disc atrophy and progression of cataract.

Patient follow-up was scheduled for every 8-10 weeks as retinal lesions were inactive (Figure 8). Nevertheless, moderate vitreous haze remained in the left eye resembling that which occurs in patients with intraocular lymphoma. It is therefore believed that both CMV retinitis and intraocular lymphoma contributed to the intraocular findings. This opinion was strongly supported in the results of vitreous fluid analysis of the right eye. Undertaking diagnostic-therapeutic pars plana vitrectomy in the left eye imposed a high risk and the patient declined this surgical procedure.

In August 2011, trepanobiopsy confirmed a transformation of follicular lymphoma into secondary acute myeloid leukemia. Palliative treatment was indicated for this disease.

At the last follow-up in March 2012, no visual acuity was recordable in the right eye (blind eye) and hand movements in the left eye. Bilateral progression of cataract prevented good fundal views although some white retinal lesions were apparent.

The patient died in another hospital in June 2012 where unfortunately no post-mortem examination was performed.

Discussion
Cytomegalovirus retinitis commonly presents in immunocompromised lymphocytopenic patients, mainly in patients with AIDS. Occurrences of CMV retinitis in immunocompetent patients although rare, have been described [9].

This report presents a case of bilateral CMV retinitis in an HIV negative patient with non-Hodgkin’s lymphoma who had a normal lymphocyte count. Intraocular inflammation of CMV aetiology occurred despite oral prophylaxis with valganciclovir. Similar cases have been published, where valganciclovir prophylaxis or ganciclovir/valganciclovir treatment were unable to prevent CMV retinitis because of drug resistance [10,11].

It is critical to differentiate lymphomatous chorioretinal infiltration from opportunistic CMV infection in order to obtain an accurate diagnosis and initiate effective treatment in patients with non-Hodgkin’s lymphoma. It is well known that the differential diagnosis of such cases should also include fulminant toxoplasmic chorioretinitis, mycotic endophthalmitis, tuberculosis, syphilis, herpes simplex or varicella zoster retinitis. Where clinical findings are not specific, intraocular fluid/tissue analysis may be necessary. Derzko-Dzulynsky et al. reported the case of a patient with follicular non-Hodgkin’s lymphoma, who developed a chorioretinal infiltrate that was initially thought to represent an intraocular manifestation of malignant disease. The patient received radiation treatment appropriate for intraocular lymphoma. The lesion progressed further and after re-evaluation, which included vitreous fluid examination, a diagnosis of cytomegalovirus retinitis was made and therapy initiated.
Figure 6 Perimetry with progression of visual fields defects. A, right eye. B, left eye.
Another case of a patient with follicular non-Hodgkin’s lymphoma and retinal infiltrate was described by Gooi et al. In this patient, CMV retinitis mimicked intraocular lymphoma and a retinal biopsy was required for assessment of the final diagnosis [13].

In the case presented here, an initial diagnostic dilemma was caused by the clinical appearance of lesions and subsequent results of vitreous fluid analysis - both of which provided evidence of CMV retinitis and concurrent intraocular lymphoma. To date, it appears that similar cases of two coexisting ocular diseases of differing aetiologies both in an active course – malignant masquerade syndrome and infectious uveitis, have not been reported. Thus, this patient was treated by means of intravenous foscarnet applied continually. However, management of non-Hodgkin’s lymphoma involved only maintenance treatment with rituximab applied every three months because of a negative restaging examination.

A therapeutic regime using foscarnet administration as a bolus three times per week was ineffective and led to a relapse of retinitis. Hence, continual intravenous application was necessary to control CMV retinitis activity. On the other hand, a study performed in patients with HIV infection showed that although foscarnet was given as a continuous intravenous infusion, there was a large variation in foscarnet concentration in the plasma of patients [14].

A suspicion remained that the persistent vitreous haze in the left eye, atypical at this degree for CMV retinitis, was an intraocular manifestation of non-Hodgkin’s lymphoma and retinal infiltrate.
lymphoma. This could not be confirmed as the patient declined vitreous fluid analysis.

Conclusions
This case reports a possible coincidence of cytomegalovirus retinitis and intraocular lymphoma in a patient with systemic non-Hodgkin’s lymphoma. The final diagnosis was based on clinical manifestations, the course of uveitis and its response to treatment as well as the results of vitreous fluid analysis. This report highlights the importance of intraocular fluid examination, especially in cases with nonspecific clinical manifestations. Such an examination allows for detection of simultaneous ongoing ocular diseases of two different aetiologies and thus enables the prompt initiation of effective treatment.

Consent
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
PS, JH, MB and ER carried out the ophthalmologic examination of the patient. All of these authors participated in management of the therapeutic approach. BK and JD performed the surgical procedure, pars plana vitrectomy. All authors read and approved the final manuscript.

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