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Original Article

Retrospective study of cytomegalovirus retinitis complicated with acquired immunodeficiency syndrome

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Abstract: Purpose: This study was designed to explore the characteristics and therapy of cytomegalovirus retinitis (CR) in patients diagnosed with acquired immunodeficiency syndrome (AIDS). Methods: A total of 67 AIDS patients (78 eyes) with CR findings of were collected from January 2009 to January 2013. The correlation between CR, cellular immunity, risk factor, clinical characteristics, treatment and prognosis of CR was assessed. The incidence of CR in different CD4+T lymphocyte count groups was analyzed. Results: Among all participants, 58 were male and 9 females, aged from 18-60 years, (38±9) years on average. CD4+ T lymphocyte count of CR patients ranged from 0-141 cells/μl and < 50 cells/μl in 81.3% of cases. CR was the primary manifestation in 10.2%, retinal lesions in 25.1%, best corrected visual acuity (BCVA) < 0.3 in 54% of AIDS patients. Retinal necrosis was involved near the posterior pole in 62.5% of CR patients. The visual acuity of 60 (47.6%) eyes was improved after treatment and 94.1% cases were cured within 3 months. Anti-CMV treatments including induction and maintenance of ganciclovir or foscarnet were discontinued when CD4+T lymphocyte count was > 150 cells/μl for three consecutive months. Complicated cataract, retinal detachment and immune reconstitution uveitis were observed in 20.5%, 12.1% and 13.1% of cases, respectively. Conclusion: Decreased CD4+T lymphocyte count is a risk factor for CR. HAART and anti-CMV therapy are efficacious treatment of CR. Conventional eye examinations should be conducted to early diagnose CR or other opportunistic infections in all AIDS patients.

Keywords: Cytomegalovirus retinitis, acquired immunodeficiency syndrome, clinical characteristics

Introduction

Cytomegalovirus retinitis (CR) is the most common ocular opportunistic infection in acquired immunodeficiency syndrome patients caused by cytomegalovirus. Bowen found that although the prevalence of CR decreases by the highly active antiretroviral treatment (HAART), the disease remains the most serious ocular complication. We concluded the information of 233 cases of Jinan Central Hospital Affiliated to Shandong University, and analyzed the clinical and laboratory data of 78 eyes of 67 patients, and explored the clinical characteristics of CR.

Materials and methods

Patients' data

The general information and clinical and laboratory data of CR patients receiving treatment in Jinan Central Hospital Affiliated to Shandong University from January 2009 to January 2013 were colleted and analyzed.

Diagnostic criteria

(1) Diagnostic criteria of AIDS: The diagnosis was made according to WS293-2008 diagnostic criteria of AIDS and infection of human immunodeficiency virus by Dujić. The HIV antibody was laboratory conformed, with an adult indications disease at least, such as HIV wasting syndrome, opportunistic infection, opportunistic tumor, *etc*.

(2) Diagnostic criteria of cytomegalovirus retinitis: retinal necrotizing lesions characterized by arcuate area of yellowish-white retinal infiltration that follows a vascular pattern with granular border and is often associated with intraretinal hemorrhages. Granular white or yellow-white exudative lesions expands slowly in mid-periphery retina, with or without retinal hemor-

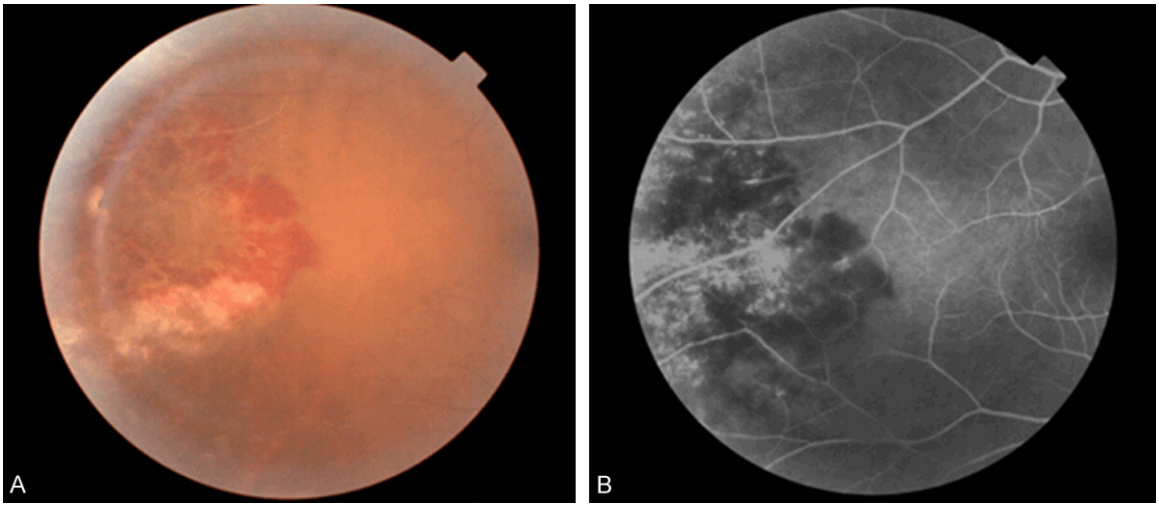

Figure 1. Fundus topography of right eye CR in AIDS patient before treatment. A: Color fundus topography, periphery retinal necrosis with hemorrhage and granular satellite lesions; B: FFA of 2A, fluorescence was covered by retinal necrosis and hemorrhage, fluorescence leakage at other lesion area.

rhage (**Figure 1**). No or mild vitreous body opacity. The CD4+T lymphocyte count is less than 200 cells/μl. Fluorescence was covered by retinal necrosis and hemorrhage in early stage of fundus fluorescence angiography, fluorescence leakage increases gradually from retinal vessels and vessel walls dyed. In late stage, fluorescence leakage at different degree was noted in lesion area.

Eye examination

Uncorrected and corrected visual acuity and intraocular tension were recorded. All patients received examination by slit lamp and funduscope tests, and partial patients underwent fundus fluorescence angiography and ocular B-ultrasound scan.

Treatment

All patients received the highly active antiretroviral treatment and anti-CMV treatment. HAART was made and supervised by physicians of infection. Anti-CMV treatment was given as soon as the diagnosis was made. As a general principle, induction therapy at an initial high dose of a drug was followed by lower dose of maintenance therapy. Intravenous ganciclovir 5 mg/kg twice daily for 3 weeks was used for induction therapy. Intravenous foscarnet 60 mg/kg three times daily for three weeks was used for those the white blood cell count decreased dramatically (< 1000 cells/ml) or bone marrow suppressed seriously. Intravenous ganciclovir 5 mg/kg or foscarnet 90 mg/kg once daily or oral ganciclovir 1.0 g, three times daily, for maintenance therapy. The maintenance discontinued when the CD4+T lymphocyte count was maintained at 150 cells/μl for three months. For relapse cases, anti-CMV treatment resumed. Ausayakhun conducted intravitreal injections of ganciclovir 2 mg/0.1 ml once a week was given to 6 eyes/6 cases who could not tolerate adverse reaction of drug, or retinopathy did not improve by systemic administration.

Follow-up

All patients were followed up. The duration of follow-up was 5 to 44 months. A majority of patients were subject to outpatient follow-up every 3 to 6 months, and others were followed up by telephone. The programs of follow-up included visual acuity, slit-lamp examination and funduscope examination.

Statistical analysis

Statistical analysis was performed by SPSS 16.0 statistical software. The CR incidence at different levels of CD4+T cell count compared by *chi*-square test, and $P < 0.05$ was considered to be statistically significant.

Results

Study subject

In the group, there were 67 AIDS patients aged from 18 years to 60 years, aged (38±9) years

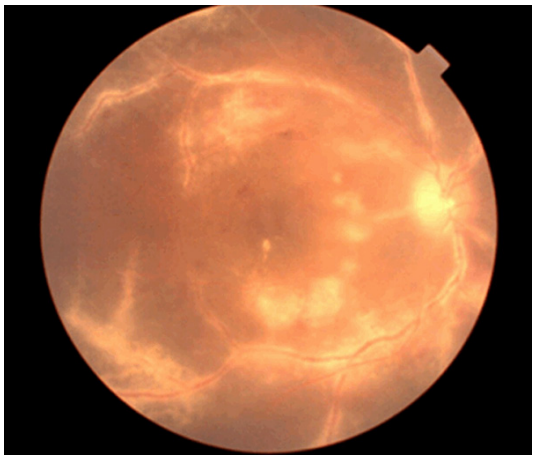

Figure 2. Color fundus topography of right eye CR in AIDS patient CR was manifested by retinal vascullitis, with serious vessel sheath and retinal necrosis.

on average. Eighty five cases were male and 9 females. Forty eight cases were infected by sexual behavior, 5 by blood transfusion, 1 by drug and 13 with unknown causes.

CD4+T lymphocyte count

No significant difference was noted between the group of CD4+T lymphocyte count ≤ 50 cells/μl and that of CD4+T lymphocyte count 50~100 cells/μl ($P < 0.05$). Significant difference was observed between the group of CD4+T lymphocyte count > 100 cells/μl and the other two groups. The CD4+T lymphocyte count was 0~141 cells/μl when CR was seen, the average count was (31.7±33.9) cells/μl. Of all, the CD4+T lymphocyte count of 77.9% cases was < 50 cells/μl, 50~100 cells/μl in 14.7% cases, the count > 100 cells/μl in 7.4% cases.

Symptoms

Among 67 cases, 50 (75.0%) consulted a doctor because of ocular discomfort, 48/50 (95.0%) cases complained of blurred vision and floater and/or visual field defect, 3/50 (5.0%) cases complained of floater only.

Ocular manifestations

(1) Thirty seven cases had bilateral CR and 30 unilateral CR. Among unilateral CR, right eyes 17 cases and left eyes 13 cases, no CR occurred in the fellow eye. The visual acuity of 31/78 eyes was below 0.05, the worst VA was no light perception in 23 patients. The VA of 29/78 eyes was 0.05~0.3 in 31 cases. The VA of 48/78 eyes was > 0.3 in 44 cases. To those who visited a doctor for the first time after 6 months the symptoms occurred, the VA of the eyes was < 0.05. The VA was < 0.3 in 33 eyes. Among them, 5 (15.6%) eyes showed extensive retinal vasculitis, the retina necrosis mainly focused on posterior pole area in 21 eyes (62.5%), serious optic neuritis and massive pre-retina hemorrhage was found in 6 (19.0%), and 1 (3.3%).

At the end of follow-up, no terminal visual acuity was observed in 9 eyes (7 binocular, 2 monocular) because of death of 11 patients. Among 78 eyes, the VA maintained 1.0 in 13 (16.7%) eyes that the initial VA was 1.0, and no visual improvement in 26 eyes (33.3%). The corrected VA improved in 39 (50.0%) eyes, and raised by 1, 2, 3, 4 and 5 lines in 21.5%, 6.5%, 4.7%, 8.4% and 6.5% eyes, respectively. The terminal VA was less than 0.05 in 28.9% eyes. The macula lutea was involved by the serious posterior pole retinal necrosis in 37.1% eyes, retinal detachment and complicated cataract occurred in 44.7% and 13.4% eyes.

Fundus manifestations

Among 78 eyes, retinal necrosis extended to more than two quadrants and one quadrant in 61.9% and 38.1% eyes. Retinal necrosis mainly occurred in posterior pole area in 33.9% eyes. The lesion of 11.9% eyes manifested as retinal vasculitis with vessel sheath (**Figure 2**). Papilledema was found in 12.7% eyes of CR with optic neuritis. Retinal hemorrhage and pre-retina hemorrhage and Roth spots appeared in 3.4% eyes CR with anemia and thrombocytopenia retinopathy related to AIDS.

Clinical outcome

The retinal lesions were alleviated after therapy. Three individuals discontinued treatment when their CD4+T lymphocyte count was < 100 cells/μl, and retinal necrosis relapsed 3 to 6 months later. Ganciclovir was given again and effective. Eight cases received intravitreal injection of ganciclovir 2 mg/0.1 ml. The duration of following-up was 3~42 months. Nine individuals died during the period. After treatment, the area of retinal lesions in 109 (86.9%) eyes became atrophy and replaced by scar with pigment disorder and linear vessels. The edema of the tissue around the retinal lesions vanished and the color returned to normal. Retinal detachment occurred in 13.1% eyes during or

after treatment. Immune reconstitution uveitis was diagnosed in 12.1% eyes because of the increasing of CD4+T lymphocyte count and the decreasing of visual acuity and serious vitreous body opacity and aggravation of retinal necrosis, including one epiretinal membrane and one cystoid macular edema. The calcification of local retinal and complicated cataract happened in 2 and 15 eyes. The papilledema faded and optic atrophy appeared in 5.6% eyes with optic neuritis. With treatment of transfusion of plasma or composition blood and HAART, the situation of anemia or thrombocytopenic individuals improved, the retinal or pre-retinal hemorrhage was alleviated gradually.

Discussion

As helper T cell, the count of CD4+T lymphocyte reflects the cellular immunity function of an individual. In our group, the average CD4+T lymphocyte count was (31.7±33.9) cells/μl when CR was diagnosed. The CD4+T lymphocyte count was lower than 50 cells/μl in 81.3% patients and 50~100 cells/μl in 15.0% of patients, while it was more than 100 cells/μl in 3.7% of cases only. It was less than 100 cells/μl in 96.3% individuals .It showed that the possibility of occurrence of CR increased while the CD4+T lymphocyte count decreased. The comparison of the CR incidence between groups of different CD4+T lymphocyte count levels showed that the incidence of CR deceased with the increase of CD4+T lymphocyte count, and that there was no significant statistically difference between the group which CD4+T lymphocyte count was less than 50 cells/μl and the group which was 50~100 cells/μl. So we believed that the CD4+T lymphocyte count lower than 100 cells/μl was a risk factor of occurrence of CR. We thought that ocular examination should be conducted to AIDS patients routinely, especially to those with the CD4+T lymphocyte count < 100 cells/μl. It should not be ignored that CR could occur in individuals with the CD4+T lymphocyte count > 100 cells/μl. Jacobson interpreted that the immune function increased by HAART was not enough to prevent CR from occurring to individuals with lower initial CD4+T lymphocyte counts.

Jacobson reported that the risk of occurrence of CR increased to AIDS patients with positive blood CMV PCR and increased CMV viral load and that the blood CMV viral load could be used as a predictor of CR. No adequate data are obtained to support this hypothesis in this study.

Main symptoms of CR included blurred vision acuity and floater and/or visual field defect. In our group, 25% patients had not any symptoms and retina lesion was found by routine ocular examination. Kempen reported the rate was lower than 54%, it indicated that the routine ocular examination was important and necessary to AIDS patients. Ocular symptom was thought as their earliest clinical manifestation in 10% of CR patients, and then they were conformed HIV antibody positive. Therefore, we thought that it should be ruled out the possibility of HIV infection for those with suspected or clinically diagnosed CR.

CR can be unilateral or bilateral. In our group, 47.5% of CR was bilateral while 52.5% unilateral, the incidence of right and left eyes was 59.5% and 40.5%. Kempen reported that CD4+T lymphocyte count and the recent months after monocular CR was diagnosed was the high risk factors of CR occurrence of the second eye. In our group, no CR occurred in the second eye for patients with monocular CR, suggesting that prompt anti-CMV therapy and HAART could prevent the occurrence of CR in the second eye. Dujic demonstrated that bilateral CR could predict the development of CMV disease and poor prognosis. In our group, two individuals had bilateral CR among 9 dead patients. However, it failed to predict correlation between bilateral CR and disease prognosis in AIDS.

Main manifestations of CR was retinal necrosis with or without hemorrhage, no or mild vitreous opacity. In our group, retinal necrosis mainly located in posterior pole area and often involved two or more quadrants. A few CR manifested retinal vasculitis. CR combined with optic neuritis and anemia retinopathy and other diseases. Clinical diagnosis was made by experienced ophthalmologist based on fundus performance and the immune status of patients.

Along with clinical treatment, majority of CR was cured clinically. The area of retinal lesions became atrophy and replaced by scar with pigment disorder and linear vessels. The edema of the tissue around the retinal lesions vanished and the color returned to normal. Retinal detachment occurred in some CR. Optic atro-

phy appeared in some CR with optic neuritis. Immune reconstitution uveitis and complicated cataract could happen in some cases with the recovery of immunity function. So we thought that CR could be cured, but Hodge suggested retinal detachment, optic atrophy, immune reconstitution uveitis and complicated cataract were poor results.

Patients received anti-CMV therapy and HAART and achieved satisfactory curative effect. HAART can inhibit the replication of HIV virus and improve immunologic function and be the foundation of effective treatment for opportunistic infection and tumor. Anti-CMV treatment includes systemic application of anti-CMV drugs and intravitreal injection gaciclovir or implantation of ganciclovir sustained-release implants. Local treatment cannot protect the second eye from infection or avoid other system infection. Hence, in our group, the intravitreal injection of ganciclovir only used for the patients who could not tolerate the adverse reactions of the drug or whose retinal necrosis with macular involvement did not obtain improvement. Glucocorticoid could be used to control the progress of the disease based on adequate anti-cmv therapy. In our group, glucocorticoid was used to treat immune reconstitution uveitis.

Three patients discontinued therapy when CR was alleviated but the CD4+T lymphocyte count was lower than 100 cells/μl and CR relapsed 3~6 months later, suggesting that although CR was quiet and immune function recovered to certain degree, the cmv virus replication was not inhibited persistently. So it was safe to discontinue anti-CMV therapy when the retinal lesion was quiet and the CD4+T lymphocyte count was > 150 cells/μl for 3 months reported by Thorne.

Sobrin demonstrated that CR caused visual damage in about 40% of AIDS patients, CR located posterior pole area caused the VA less than 0.4 in approximately 50% CR patients revealed by Holbrook. In our group, the VA < 0.3 in 54.2% of eyes when patients consulted a doctor for the first time, among them, retinal necrosis in 62.5% eyes occurred in posterior pole area. Visual acuity of 60 eyes improved to varying extents after treatment. Of which, 52.9% and 41.2% eyes received therapy within 1 and 3 months. The VA decreased or did not improve in 42 eyes after treatment. Of which 42.9% eyes received treatment for at least 3 months, indicating that vision acuity improvement was related to therapeutic intervention. The earlier the treatment given, the more likely the VA improved. The VA of 28.9% eyes damaged seriously after treatment, of which, severe vision loss in 71.3% eyes caused by retinal detachment and cataract and optic atrophy and other complications of CR, indicating that posterior pole necrosis in patients with AIDS is the leading cause of visual impairment. During follow-up, visual impairment was caused mainly by CR complications.

To sum up, CR was the most common and serious ocular opportunistic infection. The CD4+T lymphocyte count l < 100 cells/μl was a risk factor of CR. Conventional ocular examination should be performed for AIDS patients to diagnose and treat as early as possible. CR could be cured clinically. Posterior retinal necrosis and complications of CR were the main causes of visual impairment. The prognosis of vision was correlated with the time of therapeutic intervention.

Disclosure of conflict of interest

None.

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References

[1] Bowen EF, Sabin CA, Wilson P, Griffiths PD, Davey CC, Johnson MA, Emery VC. Cytomegalovirus (CMV) viraemia detected by polymerase chain reaction identifies agroup of HIV-positive patients at high risk of CMV disease. AIDS 1997; 11: 889-893.

[2] Dujić M, Jevtović Dj, Salemović D, Ranin J, Brmbolić B, Djurković-Djaković O. The prognosis of CMV retinitis among patients with AIDS in Serbia. Biomed Pharmacother 2008; 62: 443-447.

[3] Ausayakhun S, Yuvaves P, Ngamtiphakom S, Prasitsilp J. Treatment of cytomegalovirus retinitis in AIDS patients with intravitreal ganciclovir. J Med Assoc Thai 2005; 88 Suppl 9: S15-20.

[4] Jacobson MA, Zegans M, Pavan PR, O'Donnell JJ, Sattler F, Rao N, Owens S, Pollard R. Cyto-

megalovirus retinitis after initiation of highly active antiretroviral therapy. Lancet 1997; 349: 1443-1445.

[5] Jacobson MA, Stanly H, 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.

[6] Kempen JH, Jabs DA, Wilson LA, Dunn JP, West SK. Incidence of cytomegalovirus (CMV) retinitis in second eyes of patients with the acquired immune deficiency syndrome and unilateral CMV retinitis. Am J Ophthalmol 2005; 139: 1028-1034.

[7] Hodge WG, Boivin JF, Shapiro SH, Lalonde RG, Shah KC, Murphy BD, Diaz-Mitoma F. Laboratory-based risk factors for cytomegalovirus retinitis. Can J Ophthalmol 2004; 39: 733-745.

[8] Thorne JE, Holbrook JT, Jabs DA, Kempen JH, Nichols C, Meinert CL; Studies of Ocular Complications of AIDS Research Group. Effect of cytomegalovirus retinitis on the risk of visual acutty loss among patients with AIDS. Ophthalmology 2007; 114: 591-598.

[9] Sobrin L, Foster CS. Cytomegalovirus retinitis after one decade of HAART. Int Ophthalmol Clin 2007; 47: 155-164.

[10] Holbrook JT, Colvin R, van Natta ML, Thorne JE, Bardsley M, Jabs DA; Studies of Ocular Complications of AIDS (SOCA) Research Group. Evaluation of the United States public health service guidelines for discontinuation of anti-cytomegalovirus therapy after immune recovery in patients with cytomegalovirus retinitis. Am J Ophthalmol 2011; 152: 628-637, e1.