ORIGINAL ARTICLE

Cytomegalovirus Infection (CMV) in Patients with Acquired Immune Deficiency Syndrome

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SUMMARY

Cytomegalovirus infection (CMV) in patients with acquired immunodeficiency syndrome (Acquired Immune Deficiency Syndrome, AIDS) is the most common opportunistic infection. This infection is harmless for healthy individuals, but for weakened individuals cause disease. The most common form of CMV-infection in patients with AIDS is cytomegalovirus retinitis, which occurs in 15% to 40% of cases. We report the case of a man twenty-five year old, treated for CMV retinitis and retinal vasculitis vessels. Prescribed Valcyte 900 mg tbl. twice daily for 21 days with a good therapeutic effect. In patients with AIDS and decreased visual acuity is need be primarily thinking about the possible presence of CMV-infection and in time to start treatment..

Key words: Cytomegalovirus (CMV) retinitis, AIDS, valganciklovir
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INTRODUCTION

Human cytomegalovirus (CMV) belongs to the group of herpes viruses (Human Herpesvirus 5). Primary infection by human CMV takes place during life: perinatally (either in the womb or via the mother's milk), in childhood upon close contact, in adulthood through contact transmission in sexual intercourse and also through blood transfusions or blood derivates (11, 22).
Upon an increase in sexual activity in the adolescent and adult population, there is a marked increase in the number of persons with IgG antibodies against CMV (22). We know that as many as 95% of homosexual men and almost all homosexual men infected with HIV (human immunodeficiency virus) are CMV-seropositive (9, 10, 32, 41).
After the primary infection, CMV enters the latent phase, and subsequent reactivation (secondary infection) occurs depending on changes in relationships between the host and the virus (pregnancy, serious illness, stress, immunosuppressive therapy, AIDS).
Reactivation of CMV is most commonly manifested in the following: retinitis (approximately 80% of cases) and gastrointestinal disorders (colitis, esophagitis, gastritis) in approximately 15% of cases (19). Cytomegalovirus retinitis is the most common cause of loss of vision in patients with AIDS (1, 38). Less common infection manifestations of AIDS are encephalitis, pneumonia, polyradiculopathy, sclerotic cholangitis and hepatitis (11, 19, 33).

CASE REPORT

A twenty three year old man was sent to the infections clinic of the University Hospital in Hradec Králové for an eye consultation due to deteriorated vision in the right eye. He was hospitalised in the infections clinic due to clinical and laboratory progression of the base disease (infection with HIV since 2012) as a result of lack of co-operation in therapy. The quantity of CD4+ lymphocytes was equal to 80 bb/mm3L (method of flow cytometry), the viral charge of HIV 531 000 copies/ml. Data from personal anamnesis: homosexual, intravenous drug user (methamphetamine), molluscum contagiosum of the skin, candidiasis of the oropharynx and upper respiratory tracts, wasting syndrome, image of encephalitis according to magnetic resonance imaging. Overall therapy: Truvada tbl. (200 mg emtricitabine and 245 mg tenofovir disoproxil), Reyataz tbl. (atazanavir 100 mg), Norvir (ritonavir 100 mg), Mycomax tbl. (fluconazole 100 mg), Cotrimoxazol AL Forte (sulphamethoxazole 800 mg and trimethroprim 160 mg). The patient had experienced ocular complaints for 1 month as a blind spot in the visual field of the right eye, which was progressively enlarging. Visual acuity in the right eye was 2/50, correction best here, visual acuity in left eye was 6/5 naturally. Finding on the perimeter (Humphrey, test 30-2): in the right eye (fig. 1) there is absolute scotoma throughout the entire scope of the visual field, mean deviation (MD) = -33.17 dB, in the left eye (fig. 2) we find points of reduced sensitivity in the periphery, centre preserved, MD = -15.92 dB. Objectively in the right eye we find numerous precipitates on the corneal endothelium, in the anterior chamber isolated cells, turbidities in the vitreous body BIO 1+ (binocular indirect ophthalmoscopy), papilla is bordered (paler colours), on the retina there are perceptible yellowish-white areas of retinal necrosis with grainy edges, with manifestations of haemorrhage in zones 1 and 2, coarse dysgrouping of pigment, accompanying streaks along capillaries, long sections of capillaries with signs of severe vasculitis, end of vascular channel of lower temporal arcade, irregularity of vascular lumen (fig. 3). In the left eye there is a finding on the anterior segment commensurate to age, cotton wool spots predominate on the ocular fundus in the central periphery, otherwise no pathological intraocular finding (fig. 4).
Optical coherence tomography (OCT) (Zeiss Cirrus) of the central region of the right eye (fig. 5) shows reduced thickness of the neuroretina, which displays signs of necrosis and atrophy, the tissue has a hyperreflexive structure, central thickness is 76 µm.
On the basis of the objective condition, a preliminary diagnosis of CMV--retinitis was determined in the right eye, with a finding of cotton wool

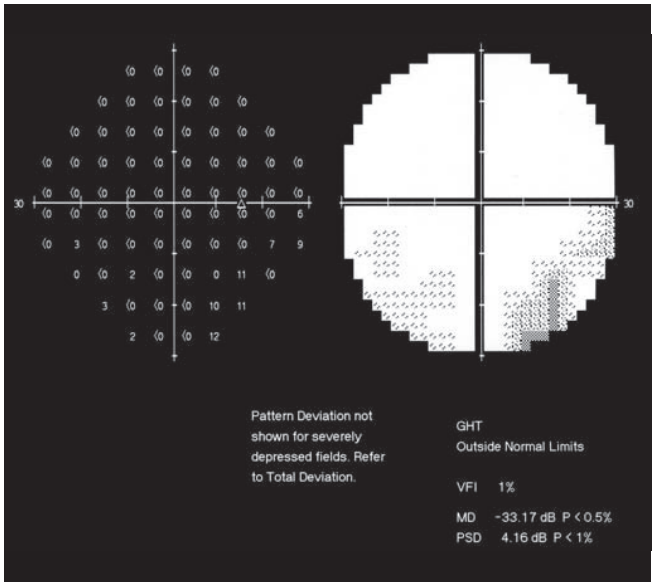

Fig. 1 Perimeter of right eye. Absolute scotoma throughout entire visual field.

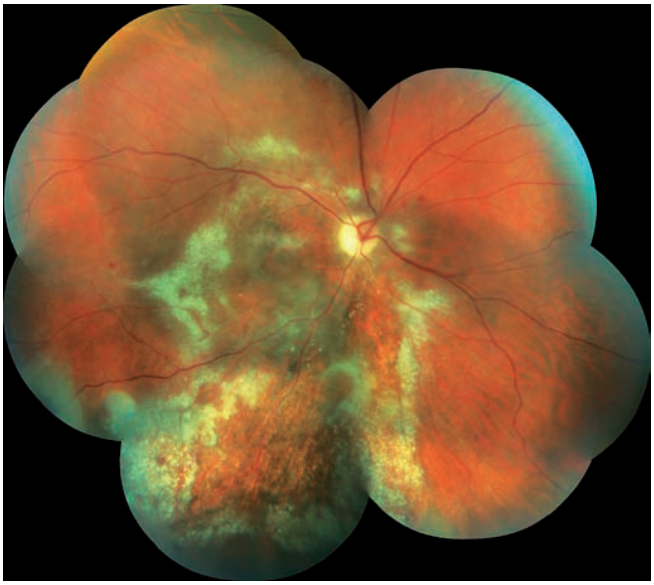

Fig. 2 Perimeter of left eye. Tunnel vision, peripheral scotoma, centre preserved.

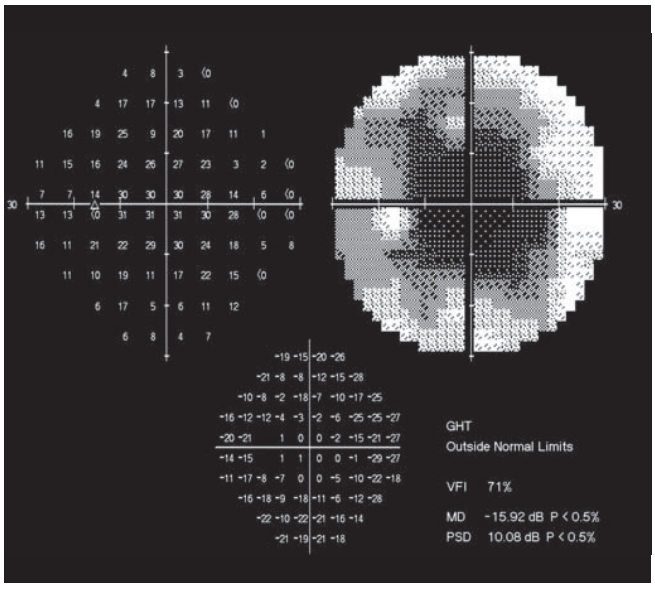

Fig. 3 Right eye. Current stage of CMV-retinitis, yellowish--white areas of retinal necrosis.

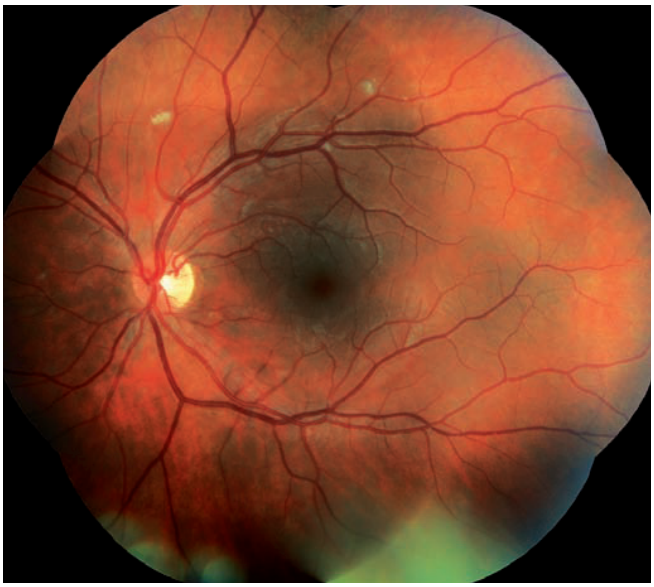

Fig. 4 Left eye. Finding of cotton wool spots.

spots on the retina of the left eye.
On the basis of the results of the laboratory values, and with regard to the finding on the ocular fundus, peroral antiviral treatment was commenced using valganciclovir (Valcyte tbl.) in a dose of 900 mg twice daily for a period of 21 days. During the following eye examinations, the clinical finding in the anterior segment of the right eye and on the ocular fundus bilaterally progressively improved (fig. 6).
At a follow-up examination at an interval of 5 weeks after the commencement of antiviral therapy, the precipitates on the endothelium and Tyndallisation in the anterior chamber of the right eye had disappeared, on the ocular fundus there was pigment hypertrophy on the border of the deposits of chorioretinal atrophy, yellowish-white retinal necroses were receding, cotton wool spots in the left eye had been absorbed (fig. 7, 8). However, atrophy of the retina is perceptible on auto-fluorescence photography of the fundus of the right eye, including the central region – coarse dysgrouping of pigment in the affected area (fig. 9). There was no improvement of central visual acuity in the right eye. The finding on the perimeter of the right eye remained without changes, with only a slight improvement in the left eye (fig. 10, 11).
With regard to the stabilisation of the finding of CMV-retinitis, the patient was transferred onto a maintenance dose of Valcyte 900 mg mg perorally once per day for a period of 3 months.

DISCUSSION

Retinitis is a serious manifestation of cytomegaloviral infection, and the most common cause of loss of sight in patients with AIDS (1, 36, 37, 38). At the time when there was not yet any specific treatment of CMV-retinitis, fears of blindness represented the most common reason for suicides amongst patients with AIDS (8).
It had previously been determined that a low quantity of CD4+ lymphocytes (T-lymphocytes, “helpers”) is a

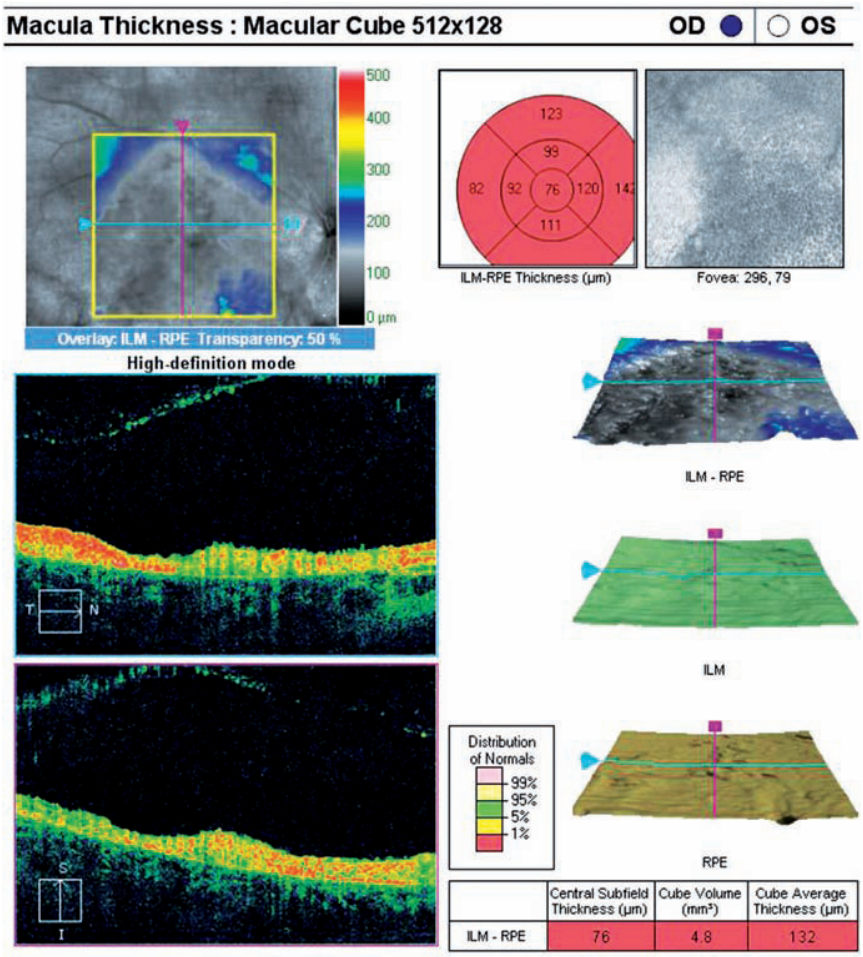

Fig. 5 OCT of right eye: reduced thickness of neuroretina, CT = 76 µm, which manifests signs of necrosis and atrophy, has hyperreflexive structure

significant risk factor for the incidence of CMV-retinitis (38, 41). A large study from the Multicenter AIDS group in the United States demonstrated that a quantity of CD4+ lymphocytes lower than 100 bb/mm3L, HIV seropositivity and homosexuality represent significant risk factors for the development of CMV retinitis (9, 19).

In the case of a reduction of CD4+ beneath the level of 100 bb/mm3L, CMV-retinita occurs in 14% of patients. If CD4+ falls beneath 50 bb/mm3L, CMV-retinitis occurs in 24% of patients (19, 45). In our case the patient had a number of CD4+ lymphocytes of 80 bb/mm3L.

Hodge et al. published a study evaluating various predictors of CMV-retinitis in patients with AIDS (23). The two most significant are previous extraocular manifestations of CMV infection (odds ratio (OR) = 82.99) and photopsia or floating turbidities in the vitreous area (OR = 11.42). Less significant predictors included experience of mycobacterial infection (OR = 3.41), finding of cotton wool spots on the retina (OR = 2.90) and homosexuality (OR = 2.83).

We determine a diagnosis of CMV-retinitis on the basis of an examination of the ocular fundus, most typically there is a presence of yellowish-white areas of retinal necrosis with grainy edges (6, 42). CMV-retinitis is spread through direct contact of the infected tissue with the adjacent healthy retina, often in the form of a “bush fire” (12). Inflammatory

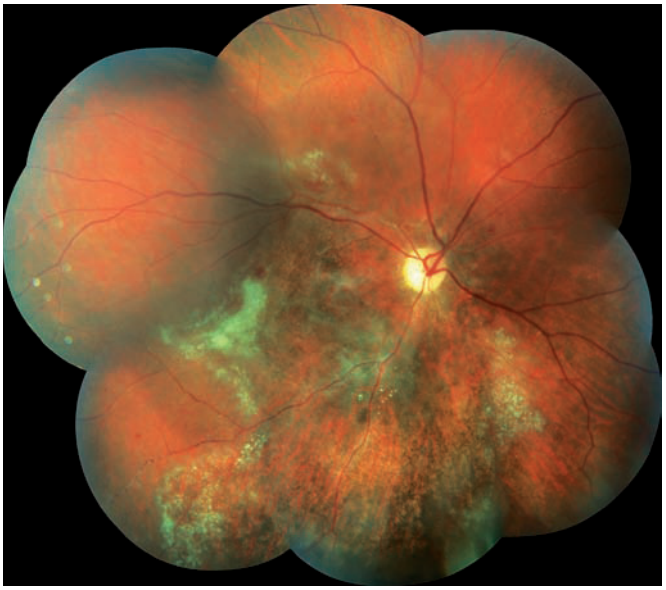

Fig. 6 Right eye. Condition 3 weeks after commencement of treatment with Valcyte. Improvement of finding.

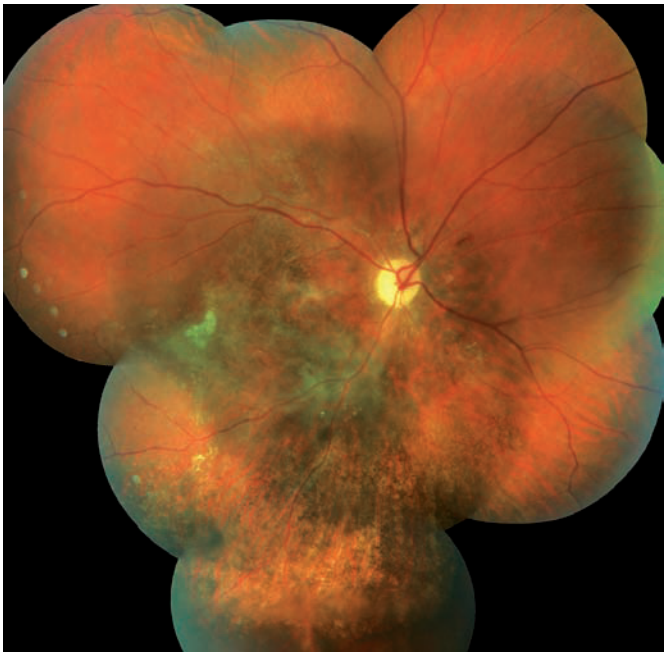

Fig. 7 Right eye. Condition 5 weeks after commencement of treatment with Valcyte. Pigment hypertrophy on border of deposit of chorioretinal atrophy and depigmentation elsewhere.

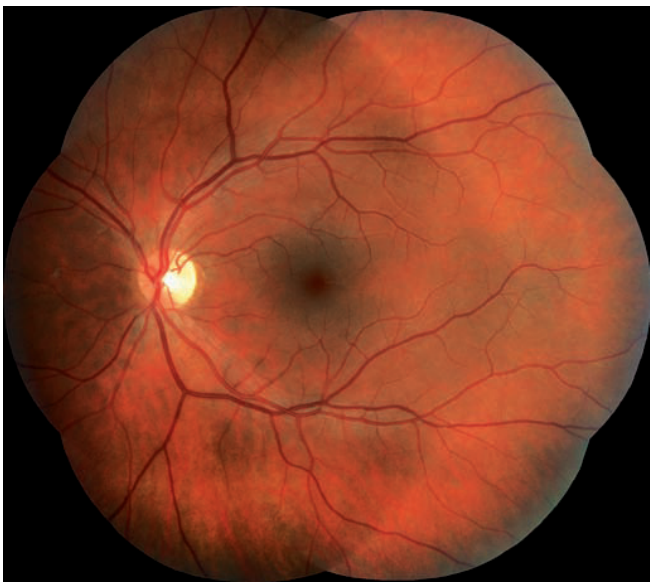

Fig. 8 Left eye. Condition 5 weeks after commencement of treatment with Valcyte. Cotton wool deposits have disappeared.

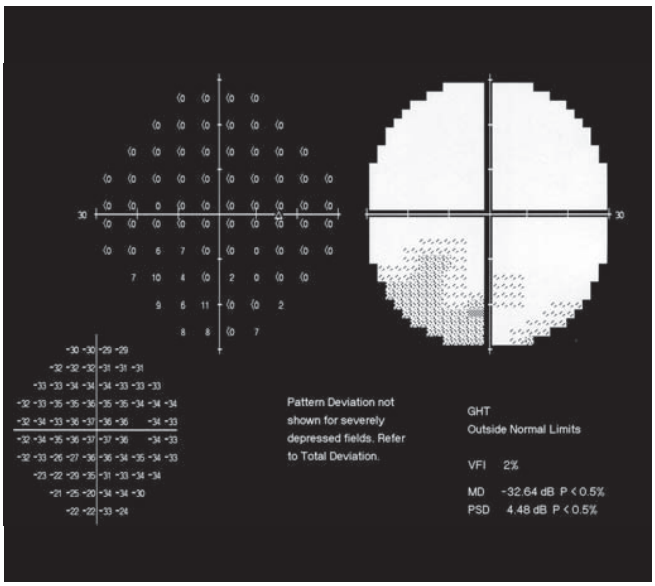

Fig. 10 Perimeter of right eye. Condition 5 weeks after commencement of treatment with Valcyte.

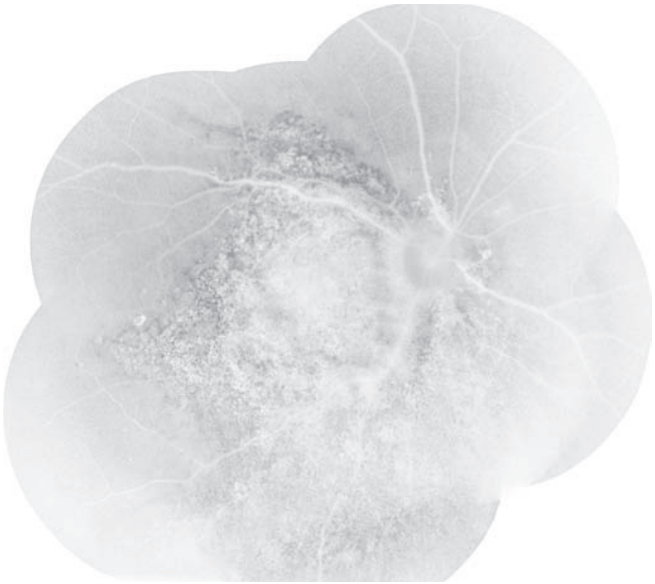

Fig. 9 Auto-fluorescence photograph of ocular fundus of right eye 5 weeks after commencement of treatment with Valcyte. Atrophy of retina including central region – coarse dysgrouping of pigment in affected area.

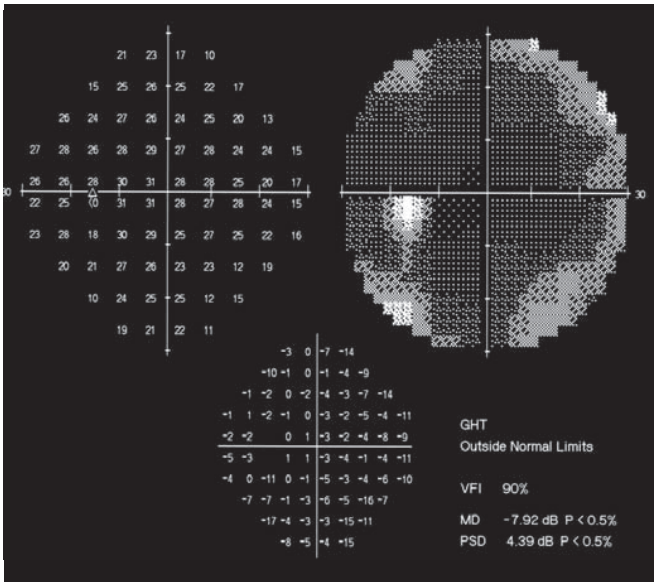

Fig. 11 Perimeter of left eye. Condition 5 weeks after commencement of treatment with Valcyte. Points of reduced sensitivity in periphery, centre preserved.

changes on the retina pass into atrophy with permanent damage to visual functions, which we recorded in our patient.

According to localisation of manifestations of CMV-retinitis on the ocular fundus, we divided the retina into 3 zones according to Lee et al. (40). Zone 1 is located 3 000 μm from the centre of the fovea and 1 500 μm from the disc of the optic nerve. Zone 2 continues from the periphery of zone 1 to the ampular vein. Zone 3 incorporates all the areas from the vortex ampullae to the ora serrata (25). The worst visual prognosis is in the case of affliction of zone 1, because this covers both the fovea and the optic nerve.

CMV-retinitis occurs most frequently in zones 2 and 3 (11, 20). Although signs of inflammation on the anterior segment of the eye and vitreous area are common, they are not so pronounced as to cause reddening, pain, anterior synechia or to impair the view of the retina, even if vitreous turbidities may progress over time (24).

Without the commencement of treatment of CMV-retinitis, a complete destruction of the retina takes place within 6 months (24). The speed of progression is relatively slow, on average 24 μm/day (27). It is important to be aware that the pathology may progress without a manifest finding of whitish deposits of necrosis on the retina, and as a result it is necessary to regularly check the ocular fundus (mainly the condition of the RPE) with applicable photo documentation.

Afflicted patients may see white stains and blind spots in the visual field, photopsia (depending on the area of the afflicted retina), floating flakes (in the case of presence of vitreous turbidities) or deteriorated visual acuity (12, 21).

There are a number of pathological con-

ditions which we have observed within the framework of differential diagnostics, accompanying the finding of CMV--retinitis in our patient. These include HIV-retinopathy, toxoplasmic chorioretinitis, acute retinal necrosis (ARN) and progressive exterior retinal necrosis.

HIV-retinopathy is characterised by a larger quantity of cotton wool spots on the retina. The prevalence of the pathology increases with the decreasing number of CD4+ cells, particularly if the value is less than 50 bb/mm3L (19, 45). It has also been demonstrated that an increased plasmatic HIV-RNA viral charge is a predictor of the development of HIV-retinopathy (17). The cause of HIV-retinopathy remains unknown, although a number of factors have been described which have an influence on the abnormal through flow of blood to the retina upon HIV-retinopathy (2, 14). Small, yellowish-white cotton wool spots appear on the ocular fundus, which represent infarctions of the layer of nerve cells in the retina and may cause the occurrence of a temporary small scotoma in the visual field, but mostly do not cause loss of sight. They are usually located in the retina around the disc of the optic nerve. Occasionally cotton wool spots may be linked to mild intraretinal haemorrhage, which leads to errors in the diagnosis of incipient CMV--retinitis. In such a case it is necessary to check the patient over the course of the following 4 weeks, when it shall be possible to distinguish HIV-retinopathy (spontaneous regression of cotton wool spots) and CMV-retinopathy (spread of original infectious deposit on the retina). In the case of HIV-retinopathy there are no manifestations of inflammation in the anterior chamber or vitreous cavity. By contrast with CMV-retinitis, the deposit of the inflammation may spontaneously disappear within a few weeks even without the commencement of therapy.

Toxoplasmic chorioretinitis may have a similar finding on the retina as CMV-retinitis (18). The only differing symptom is the degree of inflammation. In the case of toxoplasmosis, dense, opaque retinal necrosis with pronounced vitritis appear on the retina. Vitritis differs from CMV-retinitis, which usually shows minimal inflammatory manifestations in the vitreous cavity and has a dry, "granulated" border (13, 26).

Acute retinal necrosis is a rapidly progressing, vaso-occlusive, necrotising retinitis, which spreads around the perimeter of the retina. In contrast with CMV retinitis, ARN is linked with significant inflammation of the anterior segment of the eye and the vitreous cavity and occurs in both immunocompetent and immunocompromised patients. Further symptoms include neuritis of the disc of the optic nerve, scleritis and pain (28). HIV-positive patients with ARN mostly have a lower number of CD4+ cells than 100 bb/mm3L, and the ocular finding is frequently preceded by herpetic dermatological manifestations (4).

In the case of severe immunodeficiency in the later stage of AIDS, there may be secondary occurrence of progressive exterior retinal necrosis (15). However, this finding has also been reported in patients with severe immunodeficiency without HIV infection (5, 16). With the widespread use of highly active antiretroviral therapy, the number of patients with AIDS who have CD4+ T-cells lower than 50 bb/mm3L has been reduced. As a consequence of this, there has been a marked reduction in the number of new cases of opportunistic infections, including CMV-retinitis (7, 29).

Furthermore, the long-term results of CMV-retinitis point to a markedly lower risk of damage to sight upon the use of highly active antiretroviral therapy (30, 31, 35).

At present there are a number of options for treatment of CMV-retinitis that have been approved by The United States Food and Drug Administration (40). This concerns: ganciclovir administered intravenously (Cytovene-IV; Roche Laboratories Inc.), ganciclovir administered perorally (Cytovene; Roche Laboratories Inc.), foscarnet for intravenous application (Foscavir; AstraZeneca LP, Wilmington, Delaware), cidofovir administered intravenously (Vistide; Gilead Sciences, Foster City, California) and valganciclovir for peroral use (Valcyte, Roche Laboratories Inc.). There is also the option of intravitreal application of an implant which progressively releases a medicinal substance: ganciclovir (Vitrasert, Bausch & Lomb Inc., Surgical Division, Irvine, CA) and fomivirsen (Vitravene, Novartis Ophthalmics, Duluth, GA).

As an induction therapy, administration of high doses of anti-CMV drugs (antiviral drugs) is used for a period of 2-4 weeks. With regard to the fact that although the replication of CMV is suppressed, the virus is not completely eliminated from the body, further maintenance virostatic therapy in a lower dose is subsequently necessary in order to prevent the further progression of retinitis. In our case we chose valganciclovir as the induction and maintenance treatment of CMV-retinitis.

Valcanciclovir (L-valine ester ganciclovir) has good biological accessibility for peroral administration and is metabolised into ganciclovir rapidly following absorption through the intestinal wall. Peroral administration provides a similar concentration of the drug in serum as upon intravenous application of ganciclovir (34, 44).

In comparison with perorally administered ganciclovir, valganciclovir has approximately ten times higher peroral biological accessibility and provides a higher plasmatic concentration (3, 34). Valganciclovir as an induction therapy is a good alternative to intravenous administration of ganciclovir for the majority of patients with newly diagnosed CMV-retinitis, and also substitutes ganciclovir for maintenance therapy upon peroral administration (11). The most common adverse effects in connection with treatment by valganciclovir include diarrhoea (35%), nausea (23%), fever (18%), anaemia (haemoglobin < 8.0g/l) (12%) and neutropaenia (absolute number of neutrophiles < 500 cells/μL) (10%) (39). We did not record any adverse effects in our patient.

CONCLUSION

CMV-retinitis is the most common ocular manifestation of opportunistic infection in patients with AIDS.

Without timely commencement of treatment, the pathology gradually progresses and causes total necrosis of the retina and loss of sight within 6 months. Valganciclovir in peroral administration is currently a good alternative to intravenous administration of ganciclovir as both induction and maintenance therapy of CMV-retinitis.

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