

OPHTHALMIC MANIFESTATIONS OF CYTOMEGALOVIRUS INFECTION IN HIV (LITERATURE REVIEW)

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✧ Cytomegalovirus (CMV) contamination is very common: in several countries, the number of seropositive people reaches 90% among the adult population. It is a latent infection able to affect any human organs and tissues that assumes special importance in severe immunosuppression cases. Cytomegalovirus retinitis is a disabling disease, and often leads to blindness. The article deals with some issues of epidemiology, clinical course, clinical presentation characteristics of cytomegalovirus eye disease in the context of HIV-infection. A special attention is given to detection methods, problems of diagnosis against the background of immune reconstruction syndrome, treatment approaches in clinical practice, and existing recommendations.

✧ **Keywords:** cytomegalovirus retinitis; human immunodeficiency virus (HIV); HIV-infection; opportunistic disease; immune reconstruction inflammatory syndrome.

ОФТАЛЬМОЛОГИЧЕСКИЕ ПРОЯВЛЕНИЯ ЦИТОМЕГАЛОВИРУСНОЙ ИНФЕКЦИИ ПРИ ВИЧ (ОБЗОР ЛИТЕРАТУРЫ)

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✧ Инфицирование цитомегаловирусом (ЦМВ) широко распространено: в ряде стран число серопозитивных лиц достигает 90 % среди взрослого населения. Эта латентная инфекция, способная поражать любые органы и ткани человека, приобретает особое значение в случаях тяжёлой иммуносупрессии. Цитомегаловирусный ретинит является инвалидизирующим заболеванием и нередко заканчивается слепотой. В статье рассмотрены некоторые вопросы эпидемиологии, течения, особенности клинической картины цитомегаловирусного поражения глаз в контексте ВИЧ-инфекции. Особое внимание уделено методам выявления, сложностям диагностики на фоне синдрома иммунной реконституции, способам лечения в клинической практике и существующим рекомендациям.

✧ **Ключевые слова:** цитомегаловирусный ретинит; вирус иммунодефицита человека (ВИЧ); ВИЧ-инфекция; оппортунистические заболевания; синдром иммунной реконституции.

INTRODUCTION

Cytomegalovirus hominis belongs to the group of herpetic DNA-containing viruses, whose common characteristic is the capacity for long-term persistence in the body. Such persistence results

from the incorporation of the viral genome into the genetic material of the host cell [1, 2]. In 1956, it was described as type 5 herpesvirus, which turned out to be the largest herpesvirus [1]. In most cases, with normal immunity, cytomegalovirus

(CMV) infection is asymptomatic and becomes latent; under favorable conditions, however, it can reactivate rapidly. As a result of the damaging effect of the virus, giant cells are formed with intranuclear inclusions that contain replicating virus [2, 3].

EPIDEMIOLOGY OF CYTOMEGALOVIRUS INFECTIONS

Because CMV infection spreads widely throughout the body, complete elimination of the virus after initial contact is impossible. According to published data, rates of CMV infection among the adult population reach 90% [1–3]. The source is an infected person. It is transmitted sexually, through physical contact, parenterally, perinatally, and through the air [2, 3]. In primary infections, the virus is excreted from the body for several months; in cases of congenital infections, it is excreted continuously for several years. Immunoglobulin M is formed approximately 4 to 7 weeks after infection and remains in the blood for 16 to 20 weeks. Its detection during these periods may be an evidence of primary CMV infection. Then immunoglobulin M is replaced by immunoglobulin G, which remains in the blood throughout life.

According to data obtained by German researchers, the frequency of seropositivity detection increases with age [1]. In addition, the frequency of detection of CMV antibodies is related to gender (more often found in women), education level, the presence of siblings, and the presence of neighbors older than 18 years. The presence of a large number of housemates increases seropositivity rates, but residence in rural or urban areas does not have an effect [4]. In Germany, it is possible that as a result of the small number of multi-apartment high-rise buildings, urban areas are less crowded, and this may explain these results. It is known that when the infection is acquired in childhood, the virus is excreted from the body in larger amounts and for longer periods, but among persons examined in the German study, adults working with children (e. g., teachers), the rate of virus excretion was low.

Infection with CMV on a worldwide scale varies by region [1, 5]. Researchers from Mexico reported a high rate of CMV infection among pregnant women. In addition, they found that in women who were pregnant for the second time or more, a positive finding of class G immunoglobulins was more often registered. The authors attributed this to frequent contacts with children. In women pregnant for the first time, the antibody level was 15% lower. The rate

of infection detection was not affected by education level, socialization, or residence in rural or urban areas. This, as well as a number of other observations, shows the importance of hygiene skills in preventing infection. For example, ordinary hand washing before meals was found to significantly reduce the frequency of detection of antibodies to CMV [3, 5]. Thus, the data indicate that the social and material standard of living can affect the frequency of infection propagation.

EPIDEMIOLOGY OF CYTOMEGALOVIRUS RETINITIS IN HUMAN IMMUNODEFICIENCY VIRUS INFECTION

The first studies of ophthalmopathology in the human immunodeficiency virus (HIV) were conducted by Holland et al. as early as 1982. According to numerous sources, HIV-associated lesions of the structures of the eyeball and the protective apparatus of the eye were noted in 70% to 80% of infected patients [1, 3, 6, 7]. However, literature data on the frequency of ocular manifestations are highly controversial. For example, researchers from Ghana, whose observation in 2016 included patients at different stages of the disease, cited a rate of 5.8% [6]. The widespread use of highly active antiretroviral therapy (HAART), which significantly improves the prognosis of HIV-infected patients, has lowered the frequency of ocular manifestations of the infection. In addition, the rate of progression of the underlying HIV infection is associated with some alleles of the histocompatibility complex (in particular, the human leukocyte antigen C*07 allele protects against the development of CMV retinitis in HIV infection) [8].

The most pronounced antiviral effect is exerted by the lymphocytes CD4 and CD8; therefore, when the cellular immune response is inhibited, previously latent infections, including CMV infection, are reactivated. It is advisable to evaluate the incidence of ophthalmic disease in the advanced stages of HIV because its relationship with low CD4 lymphocyte counts has been proven repeatedly [1, 2, 9].

CMV-related retinitis is the most common cause of vision loss in HIV infection and, if untreated, can lead to blindness [1–3, 8, 10–12]. As a result of the introduction of HAART into clinical practice, the frequency of CMV-related retinitis decreased significantly, as has the number of severe and neglected cases [1, 8, 10]. According to some data, the frequency of retinitis has decreased by 75% [1, 10]. The timely prescription of antiretro-

viral therapy prevents the onset of deep immunosuppression (and, as a result, various opportunistic diseases) and hampers the epidemiological spread of HIV infection. It is hoped that the widespread application and early prescription of HAART will minimize the number of cases of ophthalmic manifestations of HIV infection. According to the newsletter *HIV Infection in St. Petersburg*, as of January 1, 2019, 60.1% of the patients observed received antiretroviral therapy, and this is one of the highest rates in Russia.

CMV retinitis is a hazardous complication of HIV infection. It develops under conditions of extreme immune suppression and is one of the markers of acquired immunodeficiency syndrome (AIDS). The frequency of this complication increases as the level of CD4 lymphocytes decreases; when their number is down to 50 cells/ μ L, the risk for developing CMV retinitis is extremely high [2, 6, 7, 10, 13]. In some studies, the effect of the disease stage on the development of ocular manifestations has not been confirmed [6]. This fact is inexplicable, especially because the development of opportunistic infections and their severity characterize the classifications of HIV infection by Centers for Disease Control and Prevention, generally accepted abroad, and by V. I. Pokrovsky (2001), used in Russia and the countries in the Commonwealth of Independent States. Some authors did not reveal the effect of HAART, perhaps because they did not classify patients in groups correctly (patients with a CD4 level of less than 100 cells/ μ L were not included in the sample).

Other researchers analyzed the presence of ocular disease in patients with different levels of CD4 lymphocytes (more or less than 200 cells/ μ L) [9]. According to their results, CMV retinitis did not develop in patients with a CD4 lymphocyte level of 200 cells/mL or higher (0%), whereas among patients with fewer than 200 cells/ μ L, the frequency of CMV retinitis reached 3%. The number of cases of CMV retinitis tended to increase with decreased immune status (4% of patients with a CD4 count of <100 cells/ μ L and 5% of those with a CD4 count of <50 cells/ μ L) [9]. This can be explained by the fact that CMV not only is an opportunistic infection but also contributes to the progression of HIV infection. It has been proven that the CMV protein US28 helps HIV to reduce the number of CD4 lymphocytes. At the same time, the HIV glycoprotein 120 activates CMV [2, 3]. Thus, each infection contributes to the progression of the other, forming a vicious circle.

CLINICAL MANIFESTATIONS OF CYTOMEGALOVIRUS RETINITIS

Chiotan et al. distinguished several forms of CMV retinitis [7]:

1) Typical (edematous), which is characterized by a central lesion area with edema, hemorrhages, and “filaments” of the disease propagation to the periphery of the lesion.

2) Atypical (slow), which represents exacerbation of the disease along with slow scarring and edema around old foci.

3) Perivascular, or “frosted branch” retinitis.

4) Optical neuropathy, which involves the optic nerve and CMV papillitis.

CMV retinitis can be unilateral or bilateral, and central or peripheral. The appearance of white cotton wool spots in the inner layers of the retina is characteristic; they extend into the vitreous. They occur first in one eye and then in the other, with an interval of 1 to 4 months, and the most common location is around the optic nerve; the equatorial location is less frequent. Sizes vary from 0.125% to 50% of disc diameter, and their number can vary from one or two to several tens [14]. The classical clinical presentation includes significant areas of retinal edema, extensive bushfirelike hemorrhages (as it is characterized by foreign authors), and cotton wool spots [10]. These manifestations are observed quite often in advanced cases, at a retarded visit to an ophthalmologist.

Microangiopathy is the basis of the cotton wool spots. Because the CMV is able to multiply in the endothelium, damage to the vascular wall is primary, and the retinal damage occurs later [2, 3]. The conclusions of specialists often include the term “necrotic retinitis,” which is not entirely correct but does accurately reflect the process that occurs in the retina. Edema and exudation are clinically observed, and necrosis has been noted in autopsy specimens. Other clinical forms of CMV retinitis described in the literature include the “frosted branch” type retinitis [15], in which perivascular infiltrates form around large vessels. In most cases of any variant of retinitis, the vascular bed is involved in the pathological process.

Patients with CMV chorioretinitis complain of cloudy vision, dimming or blurry vision, appearance of floaters, photopsia, and decreased central vision. Moreover, an extensive lesion with hemorrhages is often already present at the fundus [2, 3, 10, 16–18]. If treatment is initiated at this stage, it is possible to maintain intact areas of the retina, but it is impossible to restore lost visual function.

The development of retinitis in HIV-infected people occurs at different times. The process may be a slow gradual progression, with an increase in clinical manifestations over several weeks or months [10]. In other cases, CMV retinitis is fulminant (peracute), when atrophy of the optic nerve occurs 1 to 2 weeks after infection and spatial vision is lost. For slowly progressive retinitis, the presence of granular foci on the periphery of the retina is characteristic; without treatment, the lesion area increases by 1 to 3 mm per month. In the peracute course, yellow-white areas of retinal clouding, having the appearance of a geographical map, are seen [14, 19]. Sometimes, when CMV iridocyclitis is present, ciliary tenderness is noted. Iridocyclitis is usually mild but complicates CMV retinitis. Only a few cases of isolated CMV iridocyclitis have been reported [14]. Any course can be associated with a number of complications, particularly with retinal detachment [10, 16, 18].

DIAGNOSTICS OF CYTOMEGALOVIRUS INFECTION AND RETINITIS

A standard ophthalmological examination involves the use of numerous routine techniques. Indirect ophthalmoscopy in mydriasis has a special role [2, 9, 15]. Laboratory confirmation of CMV retinitis is certainly necessary, but laboratory methods have limited sensitivity, and the technical equipment of a particular medical institution may be insufficient.

In some cases of CMV, intracellular inclusions are visualized as “owl eyes” in the sediment of saliva, urine, and other body fluids [3].

In clinical practice, serum antibodies to CMV are revealed. Enzyme-linked immunosorbent assay (ELISA) confirmation of the presence of class G immunoglobulins indicates infection, but it cannot help characterize how long the disease has been present; confirmation of class M immunoglobulins, however, indicates infection activation or (more often) primary infection. For more accurate information, repeated analysis is required, as is the determination of antibody avidity, which increases over time. Interpretation of the results of these analyses in immunosuppressed patients is difficult; therefore, the detection of serum antibodies in relation to HIV infection is diagnostically insignificant [2, 16, 20].

CMV can be diagnosed by polymerase chain reaction, which allows for qualitative and quantitative analysis of virus DNA in biological fluids [2, 16, 20]. The material used is blood serum, which indicates the proliferation of CMV in the body indirectly, and in the ophthalmic fluids, such as aqueous or vitreous humor, directly. The procedure for obtaining intraocular

tissues is a surgical intervention; therefore, it cannot always be performed, especially under outpatient conditions. However, a comprehensive assessment, including data from the ophthalmoscopic examination, that accounts for concomitant diseases, HIV seropositivity, and the viral load of HIV and CD4 lymphocytes helps establishing the correct diagnosis and guide treatment.

The method for determining CMV antigenemia is ELISA, which demonstrates the presence of CMV antigens in the blood. The advantages of this technique are its relative speed (24 h) and the quantitative expression of the results. This technique has been used widely in foreign clinical practice since 1980. In Russia, this technique is rarely used. Studies conducted in South Korea suggest that the sensitivity of this method was different in HIV-positive and HIV-negative patients [21]. With leukopenia, a false-negative result is possible. The authors concluded that the data obtained with this method must be interpreted in the context of the underlying disease, clinical presentation, and ophthalmoscopy results.

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

This syndrome is a special nosological subunit of HIV infection [13, 22, 23]. It is a paradoxical immune reactivation that occurs after the start of antiretroviral therapy and characterized by the entire complement of immune responses to the antigen that has entered the body. Uveitis of the immune reconstitution inflammatory syndrome is an isolated response in that the infectious agent is not always detected by diagnostic methods, especially after prophylactic/maintenance therapy. It is supposedly mediated by the restoration of immune responses specific for residual CMV antigens in the eye [23]. To determine such a diagnosis, five criteria must be present:

- 1) AIDS.
- 2) Initiation of HAART during the AIDS phase.
- 3) Gradual increase in the number of CD4 lymphocytes, up to 100 cells/ μ L within 2 months.
- 4) History of CMV retinitis.
- 5) Appearance of a new intraocular inflammation, not associated with drug toxicity or other opportunistic infections.

The restoration of immunity with antiretroviral therapy allows some patients to discontinue anti-CMV therapy after a bout of chorioretinitis, but in some cases a chronic, poorly treatable inflammatory reaction develops. Similar manifestations are noted in patients older than 50 years at an average of 6 months after the initiation of HAART and in younger pa-

tients 2 years after initiation of HAART [23]; therefore, patients with a history of long-term CMV retinitis should be monitored by an ophthalmologist.

In immune reconstitution inflammatory syndrome, after immunity is restored, the clinical presentation may include macular edema, frosted branch angiitis, neovascularization, hemorrhage, and epiretinal membranes. The primary manifestations include anterior uveitis and vitritis. Retinal detachment, chronic iritis, and complicated cataracts of various types may develop. The speed of the immune response increases the development of complications such as cataracts or ophthalmic hypertension [13, 22, 23].

The frequency of uveitis after immune recovery may depend on the method of ganciclovir delivery to the lesion site, as selected by a specialist. For example, the intravitreal injections used by researchers in Singapore did not prevent immunorestitution reactions because they did not have a therapeutic effect on the body as a whole and did not eliminate CMV that persisted in the blood [23]. This also explains the high frequency of bilateral uveitis (77%) within the framework of this syndrome.

TREATMENT OF CYTOMEGALOVIRUS RETINITIS IN HIV INFECTION

Treatment of CMV retinitis in patients with HIV has two directions: etiotropic and restoration of immune status [13]. As immunity is restored, etiotropic treatment may be discontinued. The decision to terminate etiotropic therapy depends on many factors, such as the level of CD4 lymphocytes, a decrease in the systemic viral load of HIV, the duration of HAART, and inactivity of CMV [10]. In 1999, the U.S. Public Health Service published recommendations to discontinue the treatment in patients with stabilized retinitis when sustained immunity recovery is achieved, which is defined as a CD4 count of at least 100 cells/ μ L, after two consecutive office visits for 6 months and more [10, 11]. Clinically, CMV retinitis is considered to be stabilized if new foci are absent and the existing foci have not spread, have acquired clear boundaries, and are replaced gradually by areas of chorioretinal atrophy. Additional criteria for stabilization include decreases in uveal reaction and vasculitis.

Antiretroviral therapy in Russia is prescribed by a commission of infectious disease specialists, and the patient's condition is monitored by the attending infection diseases physician. A specialty physician, in this case an ophthalmologist, conducts etiotropic treatment and, if adverse reactions are detected, refers the patient for correction of HAART. When

prescribing treatment, ophthalmologists are guided by the general condition of the patient, whether the patient has received HAART in the past, and the synergism or antagonism of concomitant drugs, inasmuch as some drugs cause similar side effects and their combined use can lead to serious consequences.

Specific etiotropic treatment can be carried out with ganciclovir, valganciclovir, foscarnet, and cidofovir. These drugs can be administered intravenously, per os (as tablets), or intravitreally. An ocular implant that provides slow release of ganciclovir has been developed.

In the treatment of CMV retinitis in HIV infection, induction (primary) therapy is prescribed in high dosages to quickly alleviate main clinical manifestations. Supportive therapy can be prolonged, involving up to lifelong intake of the drug [1–3, 16].

The treatment methods in different regions of the world differ according to the accessibility of medical care, including specialized care, as well as the economic situation of the country [1]. Thus in South Africa, the drug is mainly administered intravitreally because this enables provision of treatment to a large number of patients [1, 10]. Studies indicate that many medical centers do not adhere to the criteria developed in the United States and by the European Clinical AIDS Society in the choice of dosage, frequency of drug administration, and timing of therapy discontinuation. Some centers develop and apply their own criteria for treatment and withdrawal; in others, the approach is individualized for each case [10].

Ganciclovir

Ganciclovir is the first-line drug used against CMV. The therapeutic dosage is 10 mg/kg/day, and it is administered by intravenous drip twice a day for 21 days. Then the dose of the drug is halved or replaced with a tablet preparation of valganciclovir. Ganciclovir has hematotoxic effects (anemia, neutropenia, thrombocytopenia) and also has teratogenic effects [1–3, 10, 16]. Systemic administration of the drug has a clinical advantage over local treatment in that it prevents both the involvement of the second eye in the infection process and the generalization of CMV infection, which can aggravate the patient's condition or lead to death [10]. The tablet preparation of ganciclovir was produced for a while, but this method of administration could not achieve a therapeutic dose in blood plasma because of its low bioavailability; therefore, it was discontinued when valganciclovir became available [1].

Viral resistance to ganciclovir results from mutations in the *UL97* viral protein kinase gene, and the frequency of resistance among patients increases in proportion to the duration of therapy (from 2.2% after 3 months to 15.3% after 18 months) [1].

Foscarnet

Foscarnet, an analog of pyrophosphate, inhibits the binding of diphosphate to the viral DNA polymerase of herpes simplex virus, herpes zoster, CMV, and HIV. The daily induction dose of foscarnet is 180 mg/kg (usually 90 mg/kg twice a day), followed by maintenance therapy of 90 mg/kg once a day [1–3, 16]. The drug is highly nephrotoxic; therefore, adequate hydration and control of creatinine in plasma are required. Resistance to foscarnet is associated with point mutations in the *polUL54* gene. Cross-resistance, both phenotypic and genotypic, between ganciclovir and foscarnet occurs in numerous viral isolates. Foscarnet is generally considered second-line therapy and is often prescribed to patients with viral strains resistant to ganciclovir or with dose-limiting neutropenia [1].

Cidofovir

Cidofovir (acyclic nucleoside phosphonate) is a broad-spectrum antiviral drug used in the treatment of CMV infection. It has high activity against CMV, papillomavirus, polyomavirus, and acyclovir-resistant herpes simplex virus. The active form of cidofovir is characterized by high intracellular stability (its half-life is more than 24 h), and so it can be used less often. The induction dosage is 5 mg/kg once a week for 2 weeks, and maintenance therapy is 5 mg/kg every 2 weeks. Resistance to cidofovir can occur (inasmuch as mutation of the gene of viral DNA polymerase, *UL54*, leads to the resistance of the virus to cidofovir, as well as to foscarnet and ganciclovir), as can the development of side effects (ophthalmic hypotension, nephrotoxicity). The pronounced toxic effect of cidofovir on kidneys limits the duration of cidofovir therapy [1].

Valganciclovir

After absorption from the intestine, valganciclovir undergoes rapid hydrolysis to ganciclovir in the intestinal mucosa and in the liver. The drug has high bioavailability (60%), therefore, it can be used in therapeutic and prophylactic concentrations [1]. Induction therapy is usually 1800 mg once a day (possibly divided into two doses) for 3 weeks, and maintenance therapy is 900 mg per day. As with the intravenous administration of ganciclovir, the dos-

age of valganciclovir should be reduced in patients with impaired renal function. Side effects include hematological disorders and dyspeptic manifestations [1–3, 16]. The use of a tablet form of valganciclovir is associated with a low incidence of viral resistance.

To prevent pronounced systemic toxic effects caused by the intravenous use of antiviral drugs, intravitreal administration is an option. Foscarnet is available as a solution; for injection into the vitreous, however, the solution can be used in only one concentration, which does not always produce a therapeutic effect. Cidofovir is not recommended for intravitreal administration. Only ganciclovir is actually used for intravitreal administration. Intravitreal injections of this drug lead to high concentrations in the retina but do not have a systemic effect. Because it is supplied as a highly soluble powder, a wide range of concentrations can be made. Repeated doses in the range of 200 to 2000 µg/0.1 mL had no toxic effect on the retina [1]. For induction therapy, the drug must be administered twice a week; maintenance therapy is administered weekly [1–3, 16].

However, this regimen has several disadvantages. Weekly injections are inconvenient for both the doctor and the patient, and there is a risk of complications (vitreous hemorrhage, retinal detachment, and endophthalmitis). Among patients in the Republic of South Africa who were given intravitreal injections, 20% suffered retinal detachment. It was also noted that the ultimate result of treatment did not depend on the number of injections, the level of initial CD4 lymphocytes, or the viral load. Instead, it was affected by the fact whether patients received HAART, by initial visual acuity, and by the amount of retinal damage [10]. In addition, as a result of the use of silicone oil during injections and an increase in the life expectancy of patients, cataracts can develop, necessitating surgical intervention; in the absence of a systemic effect, there is a risk of involvement of the second eye, the brain, and internal organs. The advantage is the likelihood of maintaining vision in case of intolerance/impossibility of systemic treatment (e. g., in cases of toxic hepatitis) [1].

Eye implants

In 1996, an eye implant that provided a slow release of ganciclovir was registered in the United States; it is surgically inserted into the eyeball. The implant with ganciclovir (“bullet”) has two shells: the outer one is a disk made of polyvinyl alcohol (PVA), and the inner one can be permeated by the drug. The drug is administered in a slow dosed

form (1 to 2 µg/hr) through the holes in the outer shell. During implantation, in the inferior temporal quadrant, in the projection of the pars plana of the ciliary body and at a distance of 4 mm from the limbus, a 6-mm-long incision is made; the implant is placed under the flap, and the flap is closed with sutures. Sometimes simultaneous partial vitrectomy is required. In this way, an intraocular therapeutic concentration is provided for 32 weeks. If further treatment is necessary after 6 to 8 months, the implant must be replaced [1–3]. The disadvantages of this method include difficult removal of the “spent” implant, which fuses with the sclera, which in turn causes complications. Sometimes the second implant is sutured in the upper temporal quadrant without removal of the first in the lower temporal quadrant. Theoretically, according to the developers, up to eight implants over the patient’s lifetime could be used.

CONCLUSION

The widespread prevalence of CMV among the adult population is associated with a high risk of this disease development in patients with HIV infection. The occurrence frequency in different regions of the world varies significantly for many reasons, particularly the economic situation of the country in general and of the patient in particular, the availability of medical care, and treatment methods. The advent of HAART has changed the epidemiological situation; the incidence of CMV infection has decreased, and the prognosis after treatment has improved. Unfortunately, the approaches to diagnosis and treatment of this serious, disabling disease are quite controversial. It is not possible to follow existing recommendations in practice in many regions, and the methods used need further improvement.

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