Cytomegalovirus infection in hematological and oncological patients receiving cytostatic therapy. Review and case report

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Summary. This review presents data of role of cytomegalovirus (CMV) in the organ pathology development in patients receiving cytostatic and immunosuppressive therapy, clinical variants of cytomegalovirus disease (CMVD), the modern possibilities of laboratory diagnosis of CMV and their practical application. Review considers approaches to the prevention and treatment of CMV-associated disease, describes etiological therapy of CMV. Clinical case of CMV pneumonia in a patient with Burkitt's lymphoma on a background of intensive chemotherapy demonstrates the difficulties in diagnosis and treatment of this complication and their impact on the success of chemotherapy.

Key words: cytomegalovirus, CMV, interstitial pneumonia, cytomegalovirus infection, cytomegalovirus disease

Introduction

Infectious complications play important role in mortality structure of oncological patients that have undergone polychemotherapy (PCT). This problem is particularly actual in oncohematological diseases treatment, where the disease itself causes significant immunosuppression. According to some authors data it may account for about 30% of all lethal outcomes at intensive, and in particular, at high-dose therapy, and competes with underlying disease mortality.

Unfortunately infectious complications problem in oncological practice remains underestimated in our country. And while bacterial infection therapy draws more attention recently, infectious complication of different etiology (viruses, protozoa, fungi) are often left out of clinicians' attention, although they are the infections that have the most severe disease course and high mortality percent, and in the recent times they occur more frequently. Adoption of high-intensive PCT schemes, including myeloablative, solid organs and hematopoietic stem cells transplantation have increased the number of patients with drug-induces immunosuppression. On the other hand introduction of antimicrobial therapy algorithms into practice reduced patients'

mortality from bacterial infections and they started to develop other, previously extremely rare infections. In the overview the evidence about mechanisms of development, diagnostics peculiarities, clinics, and approaches to cytomegalovirus infection (CMVI) treatment are presented. Case report accompanying the review is aimed to illustrate actuality of this problem in everyday practice of physician-oncologist who deals with cytostatic therapy.

Etiology, pathogenesis.

Cytomegalovirus infection primarily was described at the end of XIX century under the name "kiss disease" because it was suggested that infection is realized via saliva during kissing. The real cytomegaly "offender" – cytomegalovirus - was discovered only in 1956.

Cytomegalovirus (CMV) is DNA-containing virus of Cytomegalovirus (Cytomegalovirus hominis) genus, Herpesviridae family; its major biological feature is life-long persistence and possibility of re-activation in the organism of infected person. [15, 30] Besides this, tropism to different organs and tissues and resulting diversity of clinical manifestations are inherent to CMV. After penetration into cells *in vivo* and *in vitro* CMV causes their abnormalities. Characteristic morphological feature of CMV affected cell is cytomegaly with virus cytoplasm inclusions. At microscopic examination the effect called "owl's eye" is described. However, the morphological features described should not be regarded as organ or tissue CMV presence.

After primary infection CMV permanently remains in the body in latent form in different tissues and biological fluids. Clinical manifestation of the disease with possible severe conditions development usually takes place in immunocompromised patients, with compromised immunity more often of acquired character (e.g., at cytostatic, immunosuppressive therapy). According to different published data, the number of seropositive persons among adults is between 60 and 100% depending on region and socio-economic life conditions. [3,15] In developing countries infection of the largest part of CMV carriers takes place during childhood, while in developed countries up to 50% of young adults are CMV sero-negative [15]. Significant variations of CMV infection occur in different social groups. Thus, about 60% of USA population are CMV-positive [32], and in risk group (e.g., among homosexual men) this figure exceeds 90% [7, 12].

Cellular immunity is the most important CMV control factor in organism. Patients with disorders of cellular immune system component belong to high risk group of CMV reactivation and CMV disease development (invasive or symptomatic infection). Normal level of CMV-specific CD4+ and CD8+ lymphocytes has crucial importance in resistance to development of primary infection and CMV reactivation. During examination of patients that received allogenic bone marrow

transplantation (ABMT) it was shown that the impairment of CMV-specific CD4+ and CD8+ lymphocytes development increases CMV pneumonia risk. At the same time among the patients which received CD8+ lymphocytes infusion no cases of CMV pneumonia were reported [29].

CMV infection occurs during sexual contacts with infected person, by diaplacental infection, at virus-infected blood components transfusion or during organs or bone marrow transplantation from seropositive donors. Primary infection in seronegative individuals is accompanied by anti-CMV IgM antibodies development in 4-7 weeks after primary infection (may persist up to 20 weeks).
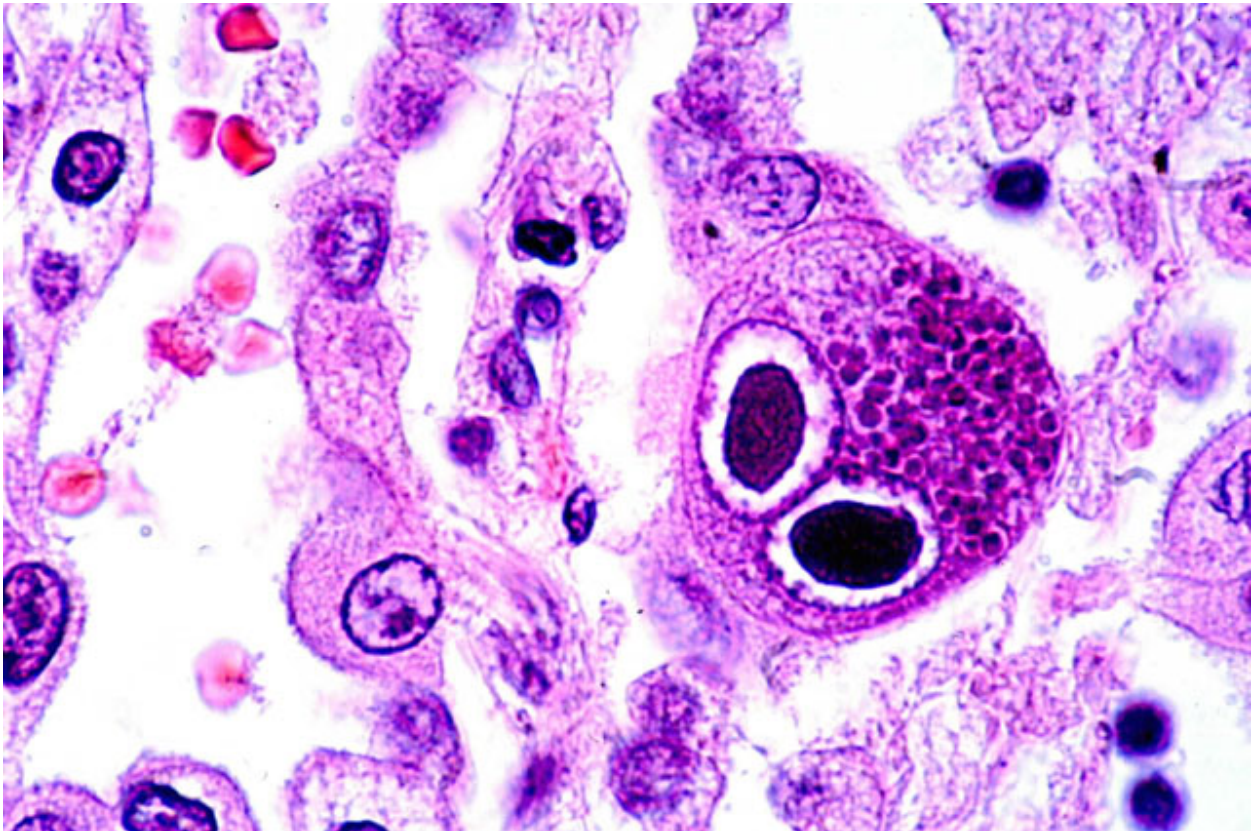

Fig. 1. Staining with haematoxylin and eosin lung tissue. Typical inclusions ("owl eyes») (× 480). Courtesy of Danny L Wiedbrauk, PhD, Scientific Director, Virology & Molecular Biology, Warde Medical Laboratory, Ann Arbor, Michigan

Clinics and diagnostics

CMV disease manifestations are diverse due to absence of tropism to any specific body tissue. Clinically significant infections usually develop in patients with some immunodeficiency degree. In immunocompetent patients CMV in majority of cases proceeds without any manifestations (asymptomatic CMVI). In patients with some immunodeficiency degree CMV in general

proceeds in a form of CMV disease (CMVD). In study of Kim et al. (2011) CMV was evaluated during liver transplantation. CMVD is a risk factor for mortality and graft rejection in recipients, and absence of such influence in persons having CMV only (virusemia) were demonstrated [16].

Risk of CMVD development in patients with oncological/hematological diseases increases when anti-cancer drugs with T-suppressive effect are used (e.g. cytarabine, high cyclophosphamide doses, methotrexate or corticosteroids) [22] or alemtuzumab, rituximab or fludarabine [10,23].

There are three major forms of CMVI [8]:

1. primary infection, when seronegative patient (that never had contact with pathogen) is infected either during contact with other patients with active infection, or by transmission of blood or tissues with latent virusemia from seropositive donors;

2. re-activation occurs in seropositive patient if his immune system becomes compromised;

3. super-infection originates in seropositive patient due to his/her infection from other patient; in this case the cause of developed infection is newly acquired virus, not the virus persisting in the host organism before.

According to the clinical manifestations distinguish latent (asymptomatic) CMVI and CMVD, i.e. development of any organ insufficiency because of CMVI. The term "CMVI" refers to detection of cytomegalovirus, its proteins or nucleic acids in body biological fluids or tissues. CMVD assumes disorder of organ/tissue function due to cytomegalovirus effect. The main problem in CMVD diagnostics is other pathogens detection and determination of their role in organ/tissue affection [18].

CMVD may be a direct result of virus affection of body tissues, or indirect effect through different mechanisms [26]. Direct CMV deleterious effect may manifest as bone marrow suppression, pneumonia, hepatitis, pancreatitis, colitis, nephritis, encephalitis, myelitis, neuropathy, retinitis or uveitis, unknown origin fewer, etc. Major indirect effects are the following: graft rejection, secondary bacterial and fungal infections, CMV associated coronary atherosclerosis in patients after heart transplantation [13].

CMVD (i.e. symptomatic CMVI) of any localization presents by impaired organ function deteriorations with appropriate clinical-laboratory profile and, in general, does not differ significantly from affections of other etiology. However, some clinical peculiarities of organ pathology allow to include CMV into differential diagnostics list. For example, cytostatic

therapy by preparations that reduce CD4+/CD8+ lymphocytes level, severe interstitial pneumonia, especially those developing on the background of adequate antibacterial and antimycotic therapy, CMV seropositive donor at bone marrow transplantation (especially if recipient is CMV seronegative) significantly increase the risk for developing of so called CMV-associated pathological process. In fact, even before the start of anticancer therapy clinician can assess the risk of CMV infection, and at possible clinical symptoms emergence - to confirm or to reject CMV origin of organ or system affection.

CMVI associated mortality is extremely low (<1%) in immunocompetent patients. However, it rises rapidly at CMVI on immunodeficiency background and appears to be significant cause in mortality structure. For example, at interstitial CMV pneumonia in patients after allogenic BMT mortality varies from 15 to 75% [15].

CMV induced pneumonia.

Pneumonia is one of the most severe complications of PCT for malignant diseases in patients having neutropenia [19]. Up to 60% of patients have pneumonia during treatment course. In study by Jain P et al (2004) among 104 patients with lung infiltrates on immunodeficiency background 26% had virus infection; at that major pathogens were CMV and herpes simplex virus [14], and also respiratory interstitial virus [28].

The most typical CMV pneumonia signs – dyspnea, blood saturation reduction, and fever. X-ray examination reveals interstitial infiltrate ("frosted glass" symptom).

The largest risk of CMV pneumonia development (up to 50%) have the recipients at lung transplantation [32].

CMV hepatitis.

Ii is characterized by increased bilirubin level that may be accompanied by enzymes levels augmentation. The diagnosis is determined by CMV presence in liver biopsy material, and also by absence of other causes of hepatitis [18].

CMV gastritis/colitis

It is manifested by clinic of appropriate GIT (gastrointestinal tract) disorder, mucous membranes affection that is detected at endoscopy after confirmation of pathological process CMV origin. For the first time CMV-colitis was described in 1985 in two homosexual men, and it is

manifested by abdominal pain and diarrhea with hemorrhage [20]. Pronounced inflammation and vasculitis may lead to ischemia and transmural necrosis of intestinal wall or stomach, and resulting perforation and peritonitis.

CMV CNS (central nervous system) affection

Diagnosis is made by CNS affection symptoms presence and CMV detection in liquor or in cerebral tissue obtained at biopsy [18].

CMV retinitis

High risk of development – is at CD4+ lymphocytes level <50 cells/μl. It is one of the most characteristic opportunistic infections in AIDS patients. Incidence of CMV-retinitis decreased after adoption of HAART therapy (Highly Aggressive Anti-Retroviral Therapy); although CMV-retinitis still remains common finding. In patients with CMV-retinitis vision acuity reduces progressively down to blindness development in the absence of therapy. At that the process can proceed as mono- or binocular. For CMV retinitis relapse prevention long-term treatment is necessary.

CMV nephritis

It is diagnosed by renal insufficiency manifestations and CMV detection at kidney biopsy. CMV detection in urine of patients with renal dysfunction is not considered as confirmation of CMV origin for kidneys affection. [18].

CMV syndrome

In patients after solid organs transplantation CMV-syndrome is determined as fever >38 °C during, at least, two days in association with neutropenia or thrombocytopenia at CMV detection in blood. Ljungman P. and co-authors proposed to avoid this term in bone marrow graft recipients considering that fever and myelosuppression may be caused by other viruses as well [18].

"Graft-versus-host" (GVHR) reaction

CMVI can be associated with acute GVHR in patients after allogenic bone marrow transplantation. Torok-Storb et al (1997) carried out an interesting study, where they examined correlation of CMV genotype gB 1-4 (variations of gene coding gB-glycopeptide) and GVHR

intensity. They demonstrated that presence of gB3 and gB4 was associated with more pronounced myelosuppression and mortality [27]. However, CMVI phenotype did not influence outcome of patients after solid organs transplantation, only mixed genotypes gB were associated with viral clearance prolongation [21].

Diagnostics of CMV aetiology is not a simple task. CMVD is accompanied by non-specific symptoms that may be common for any organ affection by any pathogen. In this situation laboratory methods are the only way to verify CMVD, clinical diagnosis of CMVD demands obligatory laboratory confirmation [9,15,17].

Since CMV in human organism can dwell in latent state, in active replication state, and can be the cause of clinically manifested pathology (i.e. CMVD), for laboratory confirmation of CMVD the fact of cytomegalovirus presence in human organism is not sufficient, it is necessary also to prove CMV etiological role in the development of organ damage. Indirect indicators of virus activity provide a chance to predict CMVD development and to start therapy on time.

For CMV detection the number of methods are available that vary in their sensitivity and specificity: cytological, serological, virological, and their modifications.

Virological examination, being the "golden standard" of virus diseases diagnostics, is rarely used due to its laboriousness and prolonged analysis.

Direct markers of CMV active replication are virusemia, viral DNA detection in blood and antigenemia.

Indirect CMVI immunological markers are the following: seroconversion (development of anti-CMV IgM and/or low-avidity anti-CMV IgG in previously seronegative persons), 4-fold and more increase of anti-CMV IgG titres in paired serums. [7] Still detection of just anti-CMV IgG does not allow to characterize period of the disease. Therefore determination of anti-CMV IgG avidity significantly increases this method value.

Among the methods of CMV antigens determination special importance have immunocytochemical method and monolayer cell culture assay ("shell vial assay"). Early and ultra-early virus antigens pp65 и pp72 are detected in blood leucocytes only in the period of virus replication. At semi-quantitative antigen pp65 detection in blood cells 25 and more positive cells in 2×105 leucocytes indicate possible infection manifestation. [4,5] Occurrence in blood of virus protein pp55 and/or major protein of ultra-early replication phase IE1 precede CMVI

clinical symptoms, therefore these markers have certain prognostic value. Disadvantages of said methods are low specificity of polyclonal antibodies, high cost of monoclonal antibodies, these methods are inferior in sensitivity to molecular methods of pathogen detection (CMV DNA), furthermore, precise pathogen amount in biological fluid is not determined.

Up to date in practice of active CMVI laboratory diagnostics increasing attention is paid to methods based on polymerase chain reaction (PCR) that allow for direct qualitative and quantitative pathogen's DNA detection in biological fluid and tissues [6]. Recent years were marked by confirmation of PCR method advantage in CMV laboratory diagnostics. Reliable criterion of cytomegalovirus high activity, proving its etiological role in the development of one or another clinical syndromes, is DNA CMV titer of 1:1000 and more in 105 leucocytes. [30,31]

CMV DNA determination in blood by PCR method also has significant prognostic importance. Gradual increase of CMV DNA in blood leucocytes and in plasma anticipates development of clinical symptoms. With every CMV DNA concentration increase in plasma by 1.0 lg the risk of CMV disease development rises three-fold. Determination of high CMV DNA concentration in blood leucocytes and plasma demands immediate start of etiotropic therapy. [3,9,25]

In that way, every of methods indicated has its disadvantages and benefits. Serological tests cannot be applied for active infection diagnostics. Cultural method is not reasonable for clinical purposes. Rapid culture method "shell vial assay" has low sensitivity. Antigen pp65 detection – is sensitive and specific diagnostics method. Real-time PCR is more sensitive and specific method (for early diagnostics) than antigen pp65 determination, and it is more reliable marker for virusemia clearance monitoring. [2,9,25,30]

Treatent of CMV associated diseases

Since CMVI and CMVD development most commonly occurs at bone marrow and solid organs transplantation, approaches to CMV problem are best of all developed for these patients group. For other patients' group receiving cytostatic/immunosupressive therapy due to oncological diseases main existing international guidelines for infections treatment either do not contain recommendations about CMV (Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer, IDSA), or extremely laconical and stipulate for only some clinical situations (Prevention and Treatment of Cancer-Related Infections Guidelines, NCCN). One of the most disputed issue is comparison of prevention and therapy effectiveness of CMV-induced diseases.

The therapy implies advance or pre-emptive therapy directed towards prevention of CMVD development.

On the one hand prophylactic anti-CMV drugs prescription may prevent CMVD development in ummunodeficiency but it significantly increases therapy toxicity and its cost. Besides this, the risk of CMVD development substantially depends on clinical situation (CMV-status of donor and recipient, transplantation type, degree of HLA compatability, etc.). At present time consensus in assessment of CMV-prophylaxis or therapy advantage has not been reached. Talking about CMV prophylaxis the important role of thorough control of transfused blood components and application of anti-leucocytes filters of IV generation should be mentioned [1].

Guidelines in infection prophylaxis and treatment in oncological patients (NCCN, 2013) recommend to provide prophylaxis of CMV or CMV disease at allogenic hematopoietic stem cells transplantation and at alemtuzumab therapy. In all other cases preventive therapy or treatment of established CMVD is indicated.

The treatment of choice for CMVD treatment and prophylaxis includes ganciclovir and valganciclovir. Other anti-virus drugs (foscarnet and cidofovir) are used as second-line therapy.

Ganciclovir is a synthetic guanine analog. It inhibits CMV replication. Its antiviral effect is caused by formation of ganciclovirthreephosphate in virus affected cells as a result of competitive DNA-polymerase inhibition and direct inclusion into viral DNA (the latter discontinues its elongation). Ganciclovir prescribed as prophylactic measure in a dose of 5-6 mg/kg intravenously every 12 hours 5 times a week for necessary period. For the treatment purpose ganciclovir is prescribed in a dose 5 mg/kg intravenously every 12 hours for 14 days. At absence of virus detection in organism the therapy discontinues. If CMV detection in biological fluids persists ganciclovir treatment is continued for 1-2 weeks.

Valganciclovir is prodrug, L-valyl ester of ganciclovir, after oral administration it is converted into ganciclovir by intestinal and hepatic esterases. For prophylaxis it is indicated orally in a dose 900 mg every day. Therapeutic dose - 900 mg twice a day, every day for 2 weeks. Additional valganciclovir prescription - 900 mg orally during 7 days after negative serological analysis is also considered.

Major side effect of ganciclovir and its prodrug is suppression of granulocitar hematopoietic lineage.

Foscarnet (phosphonoformic acid) also used for prophylaxis and treatment of CMVI, including those induced by ganciclovir-resistant strains. Preventive therapy provides by administration of 60 mg/kg 3 times a day for 14 days; supportive therapy – 90-120 mg/kg a day in single administration. Foscarnet should be prescribed with caution at kidneys function failure that is associated with pronounced nephrotoxic effect.

Cidofovir, phosphonomethyl ester of cytosine, inhibits cytomegalovirus replication by selective inhibition of virus DNA synthesis. It demonstrated high activity at cytomegalovirus retinitis treatment in patients with AIDS/HIV. It can be used for CMV pneumonia treatment, including those caused by ganciclovir-resistant strains and foscarnet-resistant strains (especially in cases of previously prophylaxis). Prophylactic dose of the drug 5 mg/kg intravenously in every 7 days. Simultaneous probenecid administration delays cidofovir elimination and significantly reduces nephrotoxicity. Therapeutic cidofovir dose is 5 mg/kg in a week for two weeks, with subsequent transfer to administration with two-weeks interval.

Anti-cytomegalovirus immunoglobulin (CMV-IG). CMV-IG is pharmaceutical drug of immunoglobulin obtained from healthy donors with high CMV titers. Its administration provides increasing anti-CMV antibodies titers. CMV-IG is usually applied in combination with antivirus agent listed above. The most frequently it is used for treatment of pneumonia, caused by CMV, in combination with ganciclovir.

Case report.

Patient S., female, 38 years old, was admitted into Oncohematology department of National cancer institute with complaints of neck tumor mass on the right side, weakness, paresthesias in right hand, headache, ambiopia. Diagnosis: Burkitt lymphoma, stage IV A. Involved regions: neck lymph nodes on the right with massive invasion of sternomastoid muscle and salivary gland, focal cerebral lesion. Bone marrow involving was not detected although thrombocytopenia of II-III degree was registered in initial blood count. Oral cavity candidosis was diagnosed on immunosupression background secondary to underlying disease and prolonged preceding glucocorticosteroids intake.

After cytoreductive chemotherapy phase by cyclophosphamide and prednisolone (for prophylaxis of tumor lysis syndrome) the therapy according to the protocol "GMALL-B-ALL/NHL 2002" was started. Also was started parallel candidosis therapy (fluconazole). First block included rituximab, high dexamethazone doses, ifosfamide, high-dose methotrexate, cytarabine, etoposide.

Toxicity according to CTC (common toxicity criteria): stomatitis of 3 degree, hematological (neutropenia and thrombocytopenia of 4 degree), febrile neutropenia. Functional impairments therapy was started according to generally accepted algorithms, granulocyte colony-stimulating factor (G-CSF) was administered in a dose 5 mcg/kg/day. While increasing the level of neutrophils diagnosed respiratory distress syndrome, lungs edema, pronounced lungs insufficiency (respiration rate up to 40/min., SpO2 85%). At CT-scans was revealed interstinal pneumonia. On the background of antibacterial therapy modification and antifungal therapy fever persisted. By PCR method CMV was twice detected in the blood. CMV pneumonia was diagnosed. Bronchoscopy for confirmation of lungs CMV infection has not been provided because of patient's severe condition. Ganciclovir therapy 5mg/kg every 12 hours was started, patient's condition started to improve up to complete reduction of respiratory insufficiency. On the background of ganciclovir therapy neutropenia (grade 4) developed, ganciclovir was interrupted, and G-CSF was administered.

After receiving twice negative CMV PCR results second chemotherapy block was commenced (rituximab, high dexamethazone doses, vincristine, cyclophosphamide, high-dose methotrexate, doxorubicin) in 31 days after planned data.

Complications of therapy: stomatitis grade 3, hematological (neutropenia and thrombocytopenia of grade 4, anemia grade 3) febrile neutropenia, gastrointestinal – diarrhea grade 3. Hyperbilirubinemia up to 73 mcM/L (due to conjugated bilirubin - up to 63 mcM/L) on the background of subnormal level of other biochemical liver markers is considered as toxic intraductal cholestasis. CMV in blood was detected (by PCR). Enteritis dominated in clinical presentation, due to this fact the patient received complete parenteral nutrition according to her energy requirements for 14 days, afterward - partial (6 days) parenteral nutrition, morphine for mucositis. Also blood components transfusion, empiric antimicrobial therapy were provided. Body mass reduced by 7 kg from initial one (12%). CMV reactivation was diagnosed (positive analysis by PCR method in blood), ganciclovir therapy recommenced. On the background of antivirus therapy positive dynamics in enteritis course was observed that was considered as indirect sign of its CMV origin. CMVI reactivation, antivirus therapy, worsening of patient's somatic state significantly delayed PCT continuation that came to be fatal in super aggressive lymphoma – was diagnosed progression of lymphoma that lead to her death.
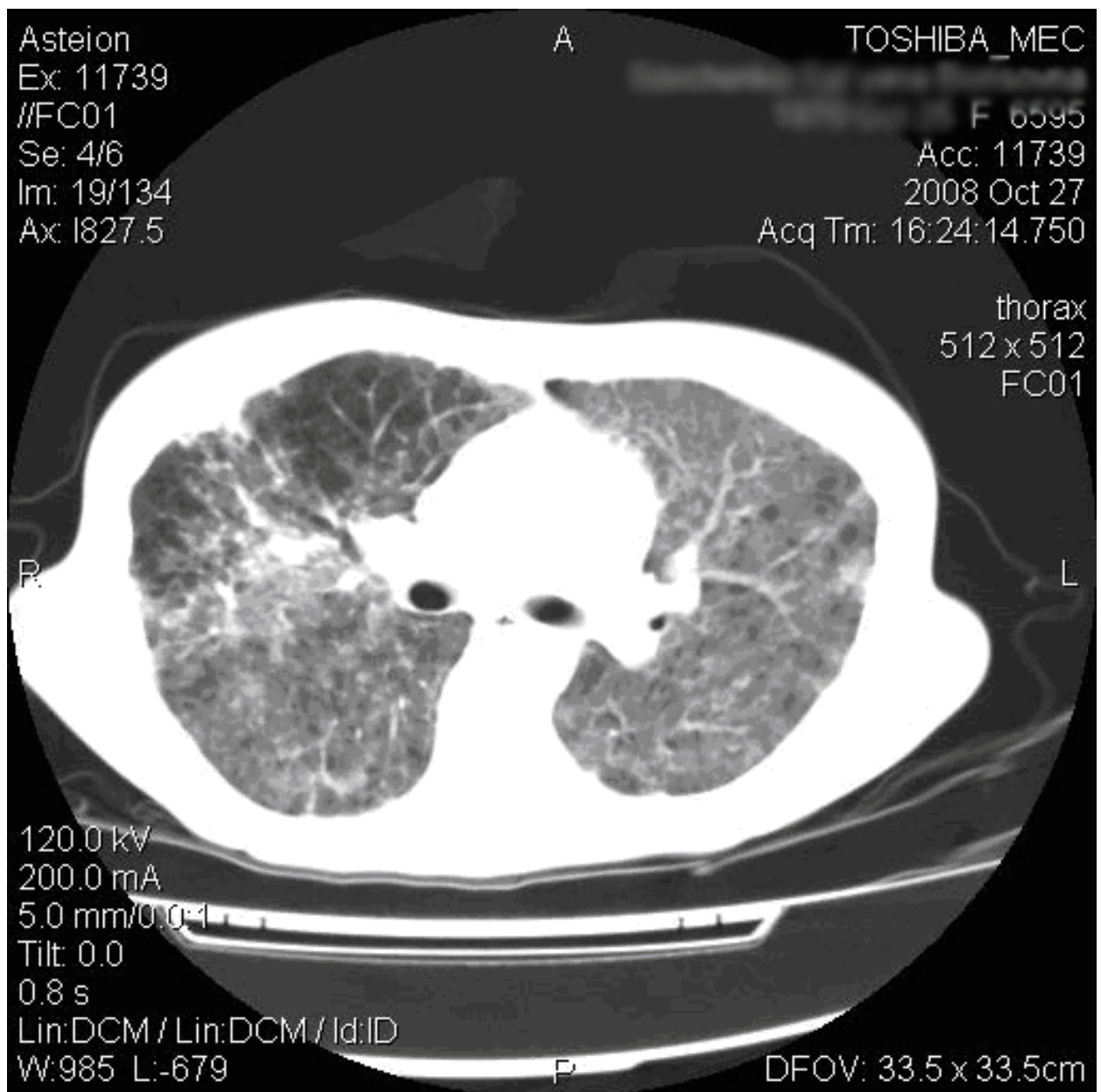
Fig. 2. Computed tomography of the lungs of the patient C.

Conclusions

CMV infection and disease are not frequently diagnosed problem in patients with malignant diseases receiving cytostatic therapy. Still CMVD development in patients with one or another immunodeficiency degree the mortality associated with CMV may reach 80% of cases.

CMV diagnostics remains complicated problem due to the fact that CMVD confirmation requires invasive procedures that often either are not available in clinic or unexecutable with regard to severe patient's state. CMV detection in organism is not a sufficient fact that confirms CMV origin of any organ affection.

Cytomegalovirus pneumonia is reluctant to treatment even with modern antivirus preparations available. At that the mortality level among patients with CMV pneumonia in patients after BMT was about 85% before administration of ganciclovir and CMV-specific immunoglobulin into practice. After these drugs using in practice the mortality reduced to 15% -75% [24].

To our opinion, optimal therapeutic strategy includes risk assessment before planning therapy and in high risk patients implementation of initial assessment of patient's infectious status (not only CMV) for more adequate empirical antimicrobial therapy could be concidered. CMV monitoring is necessary during specific therapy, and rapid therapy start in case of confirmation of its activation. However, thorough differential diagnostics of organ disfunction of other etiology is necessary, especially when histological confirmation of CMV affection is impossible. CMVI and CMVD therapy should be provided with the most active anti-CMV agents.

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