〈Case Report〉

Cytomegalovirus pneumonitis preceded infectious mononucleosis in an immunocompetent middle-aged female

Anna WATANABE, Koji KUROSE, Masaaki ABE, Daisuke YOSHIOKA
Yoshihiro KOBASHI, Toru OGA

Department of Respiratory Medicine, Kawasaki Medical School

ABSTRACT Lung involvement in cytomegalovirus (CMV) infection is uncommon in immunocompetent adult patients. In addition, when such associated findings with CMV infection are the initial manifestation before CMV infectious mononucleosis syndrome is apparent, making a correct diagnosis is difficult. Here, we experienced a rare case of CMV pneumonitis preceding CMV mononucleosis in an immunocompetent middle-aged female who needed anti-CMV treatment. She presented with fever and dry cough, and treatment with levofloxacin did not improve her symptoms. Chest computed tomography revealed diffuse ground-glass opacities over bilateral upper lobes for two weeks and she was referred to our department. Blood examinations showed impaired liver function, but no lymphocytosis or atypical lymphocytes. Serum CMV IgM and an antigenemia assay (C7-HRP) were positive, indicating an acute CMV infection. CMV polymerase chain reaction of bronchoalveolar lavage fluid was positive. The number of lymphocytes increased, and atypical lymphocytes appeared on day 11 after referral consultation; therefore, she was diagnosed with CMV pneumonitis preceding CMV mononucleosis. Anti-CMV treatment with ganciclovir improved her symptoms. Because the incidence of CMV seropositivity is decreasing in Japan, the characteristics of CMV mononucleosis are non-specific, and CMV pneumonitis may precede mononucleosis, it is important to consider CMV infection, even in immunocompetent adults, so as not to delay anti-CMV treatment if needed.

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Key words：Cytomegalovirus (CMV), CMV pneumonitis, CMV mononucleosis, Immunocompetent patient

INTRODUCTION

Human cytomegalovirus (CMV), also called human herpesvirus 5, is characterized by widespread seroprevalence, depending on the socio-economic background of the country[1]. Namely, after primary infection, CMV establishes latency in the host that can be reversed, even after many years, by numerous stimuli[1]. Thus, in adults, CMV infection should be carefully considered, especially in immunocompromised patients, human

Corresponding author
Koji Kurose
Department of Respiratory Medicine, Kawasaki Medical School, 577 Matsushima, Kurashiki, 701-0192 Japan
Phone : 81 86 462 1111
Fax : 81 86 464 1041
E-mail: kuro-ko.66@med.kawasaki-m.ac.jp

immunodeficiency virus (HIV)-infected patients, or transplantation patients, in addition to congenital CMV infection in infants, which can sometimes cause stillbirth or severe postnatal complications.

However, it is important not to neglect potential CMV infection cases in immunocompetent adults. Their symptoms are variable and usually mild, but can sometimes cause infectious mononucleosis syndrome, which is different from the highly prevalent Epstein-Barr virus (EBV)-induced mononucleosis[2, 3, 4]. In addition, although lung involvement in CMV infection is uncommon in immunocompetent patients[5, 6], associated findings that occur with CMV infection might be the initial manifestation of the disease in these hosts[2], which may make a correct diagnosis difficult. Here, we report our experience of a rare case of CMV pneumonitis preceding CMV mononucleosis in an immunocompetent middle-aged female who required anti-CMV treatment.

CASE REPORT

A 50-year-old Japanese female with a medical history of childhood asthma, gastroduodenal ulcer, and thyroiditis presented with recurred fever and dry cough for a week. She had initially presented to another hospital with symptoms of fever and back pain, which had improved after ceftriaxone and levofloxacin for 3 days were prescribed for the diagnosis of urinary tract infection. However, her respiratory symptoms began 1 week after treatment for a urinary tract infection. She was then prescribed a course of ceftriaxone and levofloxacin again for 1 week; however, her fever and respiratory symptoms failed to improve. Therefore, she was referred to the general medical department in Kawasaki Medical School Hospital. Although chest X-ray revealed no apparent abnormalities, chest computed tomography (CT) revealed dominant diffuse ground-glass opacities over bilateral upper lobes of the lungs, which lasted for 2 weeks (Fig. 1a, b). Therefore, she was referred to our department and hospitalized.

Vital signs included a heart rate of 120 beats/minute, a respiratory rate of 18 breaths / minute, blood pressure of 141/88 mmHg, SpO_2 of 97% on room air, and body temperature of 38.8℃. Physical examination revealed no tonsil enlargement, no pharyngeal redness, no swollen superficial lymph nodes, sinus tachycardia, and no abnormal respiratory sounds.

Blood examinations showed elevated white blood cell counts of 11,950/μL (69% neutrophils, 25% lymphocytes, 2.4% eosinophils), and elevated levels of aspartate aminotransferase 89 U/L, alanine aminotransferase 118 U/L, lactic acid dehydrogenase 370 U/L, C-reactive protein 2.8 mg/dL, and procalcitonin 0.16 ng/mL. Soluble interleukin-2 receptor was also elevated at 1394 U/mL, CMV-IgM (EIA) 6.9, CMV-IgG (EIA) 5.6, C7-HRP 1/50,000th. CMV and EBV serology showed

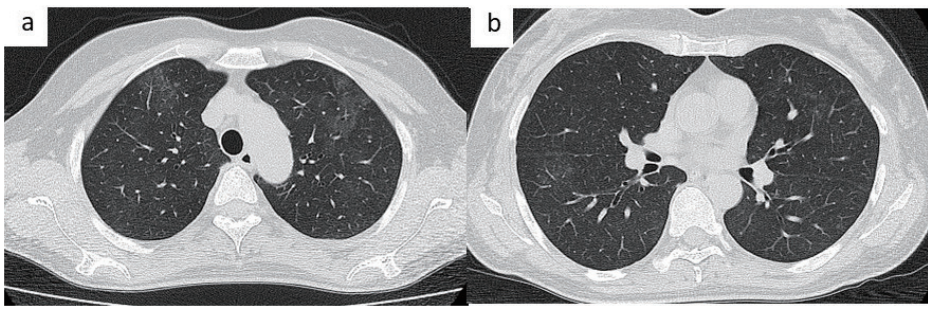

Fig. 1. a, b: Chest CT shows diffuse dominant ground-glass opacities over bilateral upper lobes of the lungs

that, in addition to positive CMV IgM and IgG, an antigenemia assay (C7-HRP) was also positive, whereas EBV viral capsid antigen IgM and IgG were negative and positive, respectively. These findings indicated an acute CMV infection and a prior EBV infection. An HIV antibody / antigen assay was negative. Autoantibody screening was negative, except anti-nuclear antibody was weakly positive with a titer of 1 : 40.

Bronchoscopy was performed to establish a diagnosis of pneumonitis. Bronchoalveolar lavage fluid (BALF) analysis showed a total cell count of 6.3×10^5/mL, a cell fraction of lymphocytes (72%), macrophages (22%), eosinophils (4%), and neutrophils (2%), and a decreased ratio of CD4 : CD8 (0.34), with negative bacterial, fungal, and mycobacterial cultures. CMV polymerase chain reaction (PCR) was positive. Histologic examination revealed the centrilobular infiltration of inflammatory cells, which mainly consisted of lymphocytes, but no intranuclear inclusion bodies (Fig. 2).

The clinical course of the patient is shown in Fig. 3. On day 11 after the referral consultation, the number of lymphocytes increased to 5318/μL (48.0%), indicating lymphocytosis, and atypical lymphocytes were present at 1440/μL (13.0%). Thus, this patient

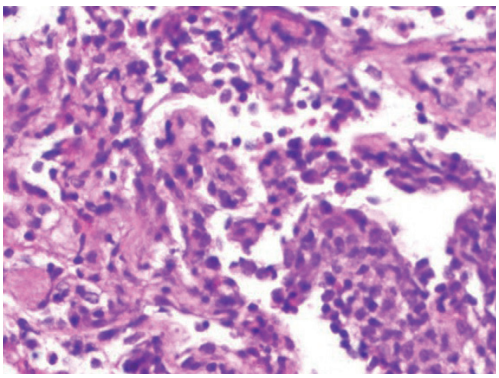

Fig. 2. Histologic examination of the lungs revealed the centrilobular infiltration of inflammatory cells, mainly lymphocytes, but no intranuclear inclusion bodies

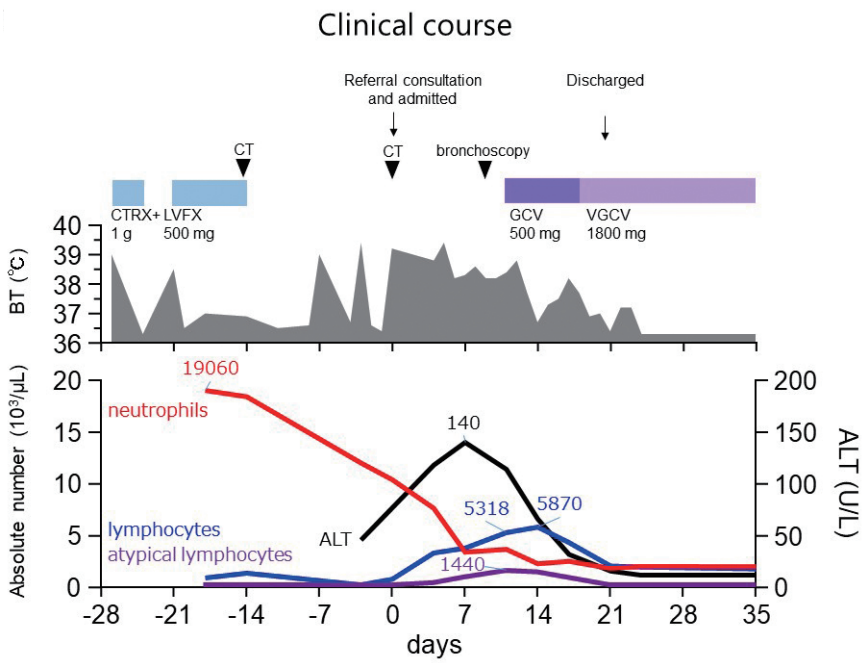

Fig. 3. Clinical course of treatment from the onset of cytomegalovirus pneumonitis
CT; computed tomography, BT; body temperature, CTRX; ceftriaxone, LVFX; levofloxacin, GCV; ganciclovir, VGCV; valganciclovir, AST; aspartate aminotransferase

was diagnosed with suspected CMV pneumonitis that occurred with CMV-induced infectious mononucleosis. Because her fever continued to be higher than 38℃ every day, anti-CMV treatment of intravenous ganciclovir (500 mg/day) was started. No neutropenia was observed. Then, her fever and impaired liver function improved. After 7 days, anti-CMV treatment with ganciclovir was changed to oral valganciclovir, and, then after 7 days, she was discharged.

DISCUSSION

We report a case in which a healthy patient presented with CMV pneumonitis preceding CMV-induced infectious mononucleosis. Complications associated with CMV infection include pneumonitis, hepatitis, Guillain-Barré syndrome, meningoencephalitis, myocarditis, thrombocytopenia, hemolytic anemia, and skin eruptions[2]. CMV pneumonitis is uncommon in healthy hosts[2, 5, 6, 7], but it is one of the most severe complications in immunocompromised hosts. Because CMV pneumonitis can precede CMV mononucleosis, as reported here, it must be considered as a differential diagnosis for pneumonitis of unknown pathogen, because it might be severe pneumonitis, which requires specific treatment[6]. It is thought that CMV invades and infects the host systemically through various body fluids, and then disseminates to the lungs, leading to secondary lung infection. However, its dissemination may be more complex[8], and infection via airway exposure may also directly cause CMV pneumonitis[5], although further research is needed to confirm this.

Histological examination with CMV inclusion bodies is characteristically used to confirm CMV pneumonitis. A previous study reported that among 12 CMV pneumonitis cases in immunocompetent adult hosts, 6 were confirmed by histology and 6 by serology[6]. Although the radiological pattern of CMV pneumonitis is variable, most cases in immunocompromised patients commonly show bilateral ground-glass infiltrates[9], which are consistent with our immunocompetent patient. Thus, the present diagnosis of CMV pneumonitis was based on positive serum CMV IgM and C7-HRP, positive CMV PCR in the BALF, radiologic patterns, and negative for other possible causes of pneumonitis, as with previous case reports[6, 7]. Although a positive PCR in the BALF alone can be supportive of CMV pneumonitis, it can be difficult to distinguish between CMV pneumonitis and pulmonary CMV DNA shedding[10, 11].

Although seroprevalence is high in some populations, a high percentage of women of reproductive age are still CMV seronegative, and thus are at risk of primary CMV infection during pregnancy[12], leading to a higher rate of transmission to fetuses. Of note, improvements in public health have led to a decrease in the seroprevalence of maternal CMV IgG antibodies among Japanese women from 69.9% in 2003 to 65.2% in 2012[13], which may indicate an increase in primary CMV infections in the future. She is also thought to be in primary CMV infection. Thus, although preventive medicine including vaccination is important, CMV infection should be considered as a differential diagnosis even in healthy adults.

Most infectious mononucleosis cases are estimated to be caused by EBV (72% - 79%), with the other cases being caused by CMV (21% - 27%)[3, 4]. Although a sore throat with enlarged exudate-covered tonsils is more common with EBV infection, fever may predominate, and signs of enlarged lymph nodes or splenomegaly may be rarely noted in CMV infection[2, 3, 4], which is consistent with the present case. Thus, fever, low-level liver function abnormalities, and lymphocytosis with increased numbers of atypical lymphocytes in the absence of severe tonsilitis and lymphadenopathy are characteristic of CMV mononucleosis, which

is different to EBV mononucleosis. Therefore, we should carefully consider the non-specific symptoms in CMV mononucleosis cases.

Here, we reported the case of a healthy female who developed CMV pneumonitis preceding CMV mononucleosis and who recovered after anti-CMV treatment. CMV infection in immunocompetent patients tends to be neglected because of the seemingly high prevalence of CMV seropositivity or presence of relatively mild symptoms. However, taking into consideration the decreasing tendency of CMV seropositivity and the poorly defined characteristics of CMV mononucleosis and CMV pneumonitis in the absence of mononucleosis, we should consider CMV infection even in immunocompetent patients so as to not delay anti-CMV treatment if required.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This case report has obtained approval by the Medical Research Ethics Committee of Kawasaki Medical School and informed consent from the patient prior to data collection and assembling.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Anna Watanabe: Investigation, Writing - Original Draft. Koji Kurose: Investigation, Writing - Review & Editing. Masaaki Abe, Naoya Yasokawa, Daisuke Yoshioka, Yoshihiro Kobashi: Acquisition of data. Toru Oga: Conceptualization, Supervision, Writing - Review & Editing.

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CONFLICT OF INTEREST

The authors declared that there is no competing conflict of interest

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