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Original Article

Factors associated with cytomegalovirus antigenemia in patients with rheumatic disease: A retrospective study

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ABSTRACT

Introduction: This study aimed to examine the factors associated with cytomegalovirus (CMV) antigenemia and the time of onset of CMV antigenemia among patients with rheumatic diseases.
Methods: A single-center, retrospective, observational study was conducted in our institution from January 2009 to December 2017. This study included patients with rheumatic diseases who had at least one CMV antigen measurement. Multivariate analysis and receiver operating characteristic analysis was performed.
Results: A total of 249 patients underwent CMV antigenemia assay, and 84 (33.7%) patients tested positive. When the association between CMV antigenemia and possible associated factors was investigated, multivariate analysis showed that daily steroid dose increased the odds of having CMV [odds ratio 16.25, 95% confidence interval (CI), 5.360–49.253]. In this study, the cutoff value of daily steroid dose found in this study (0.45 mg/kg/day) was reasonable in clinical practice, and the area under the curve of the steroid dose was 0.838 [95% CI 0.781–0.882], which was the largest of the known indicators. Moreover, the median time from the start of immunosuppressive therapy to the onset of CMV antigenemia was 30 (interquartile range, 21–44) days, and most of the daily steroid users (85.7%) developed CMV antigenemia within 60 days.
Conclusions: The daily steroid dose is the most important factor associated with CMV antigenemia. Therefore, monitoring and treatment strategies based on the steroid dose, especially in the initial 2 months, are important.

1. Introduction

Cytomegalovirus (CMV) is reactivated occasionally in patients with immunosuppression and becomes a leading cause of fatal complications [1]. CMV disease in adults occurs in patients who have undergone hematopoietic stem-cell transplantation or solid-organ transplantation, have advanced human immunodeficiency virus infection, are receiving immunosuppressive therapy, or are critically ill and require intensive care [2–5].

The definitive diagnosis of CMV disease requires the presence of cytomegalic cells with intranuclear inclusion bodies and inflammation in the histological findings of the infected organs. However, biopsy may be difficult in some cases because of the patient's condition, and diagnosis should be often made comprehensively based on clinical symptoms and blood test findings. The CMV antigenemia assay has a high sensitivity and specificity of ≥85% and correlates well with clinical symptoms and course [6,7]. The CMV antigenemia assay is a useful indicator for determining the timing of initiation and discontinuation of antiviral drugs and the efficacy of treatment because a positive result can be obtained before the development of CMV disease. Therefore, the assay is used to monitor CMV infection in patients who had undergone transplantation. Preemptive therapy employs a strategy of administering an antiviral drug when CMV is detected to prevent the development of CMV disease [8,9]. Regular CMV surveillance is recommended for patients who had undergone hematopoietic stem-cell or solid-organ transplantation as an indicator to consider preemptive therapy [10,11].

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; AUC, area under the curve; CMV, cytomegalovirus; DM/PM, polymyositis/dermatomyositis; ROC, receiver operating characteristic curve; SLE, systemic lupus erythematosus.

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With the introduction of preemptive therapy, the incidence of CMV disease, especially CMV pneumonia, has been reduced drastically [12,13]. Furthermore, the incidence of CMV disease within 100 days of transplantation has been reported to have decreased from ≥30% to <10% [14].

In patients with rheumatic diseases, CMV infection is a major opportunistic infection with high morbidity and mortality rates [15,16]. Reported risk factors of CMV reactivation in patients with rheumatic diseases include low lymphocyte count, hypoalbuminemia, high CMV antigen-positive cell count, systemic lupus erythematosus (SLE), dermatomyositis/polymyositis (DM/PM), antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, immunosuppressive therapy, daily oral corticosteroids, steroid pulse therapy, intravenous cyclophosphamide, oral candida, and pneumocystis pneumonia [17–22]. Various factors have been identified; however, further studies are required to fully understand CMV reactivation. In actual clinical practice, patients with rheumatic disease undergoing immunosuppressive therapy are monitored for CMV and are considered for preemptive therapy, as are patients who underwent transplantation; however, knowledge on patients at a high risk, their management, and optimal duration of monitoring is limited.

Owing to recent advances in treatment, the number of diseases that require immunomodulators, including high-dose steroids or biological agents such as DM/PM and ANCA-associated vasculitis, is rising, and the potential for CMV infection has been increasing. Further research is warranted, but only a few small-scale studies are conducted because of the variability of rheumatic diseases. In this study, we focused on steroid dosage among the factors associated with CMV infection. The frequency of CMV infection is generally reduced after the steroid dose is lowered with or without immunosuppressive agents. Moreover, SLE, DM/PM, and vasculitis, which are considered to pose a high risk, are also a group of diseases that require high-dose steroid therapy. Therefore, a large-scale observational study of rheumatic diseases in general was conducted to examine the factors associated with CMV infection and the time of onset of CMV antigenemia among patients with several rheumatic diseases.

2. Patients and methods

2.1. Study design and data collection

This was a single-center, retrospective, observational study. Data of all patients with rheumatic diseases who had undergone CMV antigenemia assay were reviewed at the Departments of Clinical Nephrology and Rheumatology and Respiratory Medicine and Infectious Diseases, Niigata University. Adults aged ≥18 years who had at least one CMV antigenemia measurement between January 2009 and December 2017 and could be followed up for ≥5 years through medical records were included. Patients' background, medication history (steroids, immunosuppressive drugs, and biologics), and blood test data were collected from electronic medical records. Steroid doses and blood test data were collected at the time point of CMV antigen measurement. If the CMV antigen was measured more than once, the time point of the first positive result was used for positive cases, and the time point of the highest steroid dose administered was used for negative cases. At the discretion of the attending physician, treatments such as steroid therapy and antiviral drug administration were conducted. CMV antigenemia was defined as the detection of at least one positive cell in the CMV antigenemia assay. CMV antigenemia has been classified into CMV infection and CMV disease [23]. CMV infection is a condition in which CMV is identified in the body through blood or other specimens, and CMV disease is defined as reactivation of CMV accompanied by clinical symptoms and organ damage.

2.2. CMV pp65 antigenemia assay

CMV antigenemia assays use monoclonal antibodies to bind to pp65 antigen, a structural protein that appears very early after leukocyte (mostly neutrophil) infection with CMV, followed by staining and microscopic examination. At our hospital, a kit (LSI Medience Corporation, Tokyo, Japan) that utilizes C10/C11 as monoclonal antibodies was employed. In the C10/C11 method, approximately 150,000 polymorphonuclear leukocytes are fixed and stained on one slide; two slides are prepared, the entire field of view is observed under an optical microscope, and the number of CMV pp65 antigen-positive cells is visually counted and reported.

2.3. Ethics statement

This study complied with the principles of the Declaration of Helsinki and the current ethical guidelines and was reviewed and approved by the Ethics Committee of Niigata University (Approval No. 2017–03879). Because this study used data from existing electronic medical records, the requirement for written informed consent was waived. The purpose of the study and the opportunity to opt out were provided on the Niigata University website.

2.4. Statistical analysis

All statistical analyses were performed using JMP13.0.0 (SAS Institute Inc., Cary, NC). Data are provided as median and interquartile range (IQR) for continuous variables and percentage (%) for categorical variables. The *t*-test was used for continuous variables with normal distribution, Wilcoxon's rank-sum test for continuous variables with non-normal distribution, and the chi-square test for categorical variables. The Cochran–Armitage trend test was used to test for trends in CMV antigenemia, daily steroid dose, and total steroid dose. Multivariate analysis was performed, including the factors that were significantly different between the two groups (Table 1). The cutoff value for each factor was determined by creating receiver operating characteristic curve (ROC) and using the Youden index. In actual clinical practice, lymphocytes and IgG may be monitored as indicators of CMV reactivation [24]. Therefore, to evaluate the strength of the association of CMV antigenemia with the steroid dose, lymphocyte count, and IgG, the area under the curve (AUC) was compared using the ROC curve. A logistic regression model was used to evaluate the association between CMV antigenemia and the associated factors. P-values of <0.05 were considered significant.

3. Results

3.1. Characteristics of the patients

A total of 249 patients with rheumatic diseases underwent CMV antigenemia assay, and 84 (33.7%) and 165 (66.3%) tested positive and negative for CMV antigen, respectively. In the antigen-positive group, the median age of the patients was 64 (IQR 50–72) years, and a smaller proportion (35.7%) was accounted for by male patients (n = 30). Rheumatic diseases included rheumatoid arthritis (RA) in 59 (23.7%), SLE in 57 (22.9%), vasculitis in 43 (17.3%), DM/PM in 27 (10.8%), systemic sclerosis in 16 (6.4%), mixed connective tissue disease in 11 (4.4%), adult-onset Still's disease in 9 (3.6%), Sjögren syndrome in 6 (2.4%), Behçet's disease in 5 (2.0%), and others in 16 (6.4%) patients (Table 1). Regarding the treatment of the primary disease in the CMV antigen-positive group, 40 (47.6%) patients were treated with steroid pulse therapy, 32 (38.1%) with immunosuppressive drugs, and 0 with biologics. The steroid dose at the time points of CMV antigen measurement in the CMV antigen-positive group (45 mg/day; IQR 35.0–60.0) was significantly higher than that in the CMV antigen-negative group (15 mg/day; IQR 7.5–40.0) in the prednisolone

Table 1
Characteristics of the patients.

	CMV antigenemia assay (n = 249)		
	Positive (n = 84)	Negative (n = 165)	p value
Age (years), median (IQR)	64 (50–72)	62 (44.5–70)	0.3213
Sex (males)	30 (35.7)	40 (24.2)	0.0732
Weight (kg), median (IQR)	52.5 (45.59–60.73)	50.4 (44.75–57.60)	0.107
Underlying disease			
Rheumatoid arthritis, n (%)	10 (11.9)	49 (29.7)	0.0016
Systemic lupus erythematosus, n (%)	25 (29.8)	32 (19.4)	0.0794
Vasculitis, n (%)	17 (20.2)	26 (15.8)	0.3807
Dermatomyositis/ polymyositis, n (%)	16 (19.0)	11 (11.5)	0.0046
Systemic sclerosis, n (%)	3 (3.6)	13 (7.9)	0.2756
Mixed connective tissue disease, n (%)	4 (4.8)	7 (4.2)	1.0000
Adult-onset Still's disease, n (%)	4 (4.8)	5 (3.0)	0.4909
Sjogren syndrome, n (%)	1 (1.2)	5 (3.0)	0.6668
Behcet's disease, n (%)	1 (1.2)	4 (2.4)	0.6655
Others, n (%)	3 (3.6)	13 (7.9)	0.2756
Diabetes mellitus, n (%)	34 (40.5)	29 (17.6)	0.0310
Steroid pulse therapy, n (%)	40 (47.6)	28 (17.0)	<0.0001
Immunosuppressive drugs, n (%)	32 (38.1)	51 (31.0)	0.2596
Biological agent, n (%)	0 (0.0)	11 (6.7)	0.0178
Prednisolone equivalent dose (mg/day), median (IQR)	45 (35.0–60.0)	15 (7.5–40.0)	<0.001
Prednisolone equivalent dose (mg/kg/day), median (IQR)	0.90 (0.64–1.11)	0.30 (0.17–0.75)	<0.0001
White blood cell count (/μL), median (IQR)	7265 (4880–10605)	9060 (6770–11415)	0.0073
Neutrophil count (/μL), median (IQR)	5995 (3534–8393)	6900 (4818–9515)	0.0596
Lymphocyte count (/μL), median (IQR)	931 (552.5–1510.0)	1419 (900.5–2025.0)	0.0019
Hemoglobin (g/dL), median (IQR)	11.7 (9.13–13.20)	11.3 (9.95–12.60)	0.6855
Platelet count ($\times 10^4$/μL), median (IQR)	16.4 (12.13–22.23)	24.6 (19.00–30.05)	<0.0001
Albumin (mg/dL), median (IQR)	3.1 (2.6–3.5)	3.3 (2.8–4.7)	0.0476
AST (U/L), median (IQR)	24 (18.0–39.0)	23 (17.0–30.5)	0.6744
ALT (U/L), median (IQR)	40 (22.3–67.5)	20 (13.0–32.5)	0.0876
LDH (U/L), median (IQR)	274 (210.3–366.0)	217 (182.0–296.5)	0.0038
ALP (U/L), median (IQR)	194 (160–241)	182 (148–256)	0.807
Creatinine (mg/dL), median (IQR)	0.73 (0.55–1.02)	0.64 (0.53–0.90)	0.4608
CRP (mg/dL), median (IQR)	0.13 (0.04–0.94)	0.79 (0.08–4.78)	0.0028
IgG (mg/dL), median (IQR)	861 (675–1280)	1171 (779–1550)	0.004

CMV, cytomegalovirus; IQR, interquartile range; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; CRP, C-reactive protein.

equivalent amount (Table 1). Furthermore, the Cochran–Armitage trend test for CMV antigenemia and steroid dose showed that the number of CMV antigenemia-positive cases increased significantly as the steroid dose increased (Fig. 1a). Significant differences in leukocyte count, lymphocyte count, platelet count, albumin, lactate dehydrogenase (LDH), C-reactive protein (CRP), and IgG were observed between the two groups in the blood tests performed at the time point of CMV antigen measurement (Table 1).

In 38 cases, antivirals were used to treat CMV disease or as a preemptive therapy against CMV antigenemia. The incidence of CMV disease was unclear because sufficient evaluation of organ lesions was not performed in all cases. We performed additional analysis to investigate the characteristics of cases for which treatment was decided by the attending physician. Even when the results were compared with and without antiviral drug administration, they were similar to those for CMV antigenemia (Supplemental Table S1).

3.2. Number of days from treatment initiation until the CMV antigen becomes positive, total steroid dose, and CMV antigenemia

The time from the initiation of new immunosuppressive therapy to the onset of CMV antigenemia and the association between CMV antigenemia and total steroid dose in patients with rheumatic diseases were also investigated. Steroid therapy was newly initiated in 71 patients with rheumatic diseases, which included 35 (49.3%) CMV antigen-positive and 36 CMV antigen-negative cases. The median time from the start of treatment until the CMV antigen became positive was 30 (IQR 21–44) days. Positivity was achieved in 18 (51.4%) patients within 30 days and in 30 (85.7%) within 60 days (Fig. 1b).

The total steroid dose (total steroid dose administered between treatment initiation and December 2017, the time point of the last CMV antigen measurement) was calculated, and as for prednisolone, the median dose was 5545 mg (IQR 2810–11236) and 3899 mg (IQR 1959–13143) in the CMV antigen-positive and CMV antigen-negative groups, respectively. No significant correlation was found between the Cochran–Armitage trend test for the total steroid dose and CMV antigenemia (Fig. 1c). These results indicate that for steroid doses, the current dose, not the total dose, is the most important and relevant factor.

3.3. Multivariate analysis and ROC analysis

In Table 1, the multivariate analysis of factors displaying significant differences between the two groups showed that the adjusted odds ratio (OR) for prednisolone (≥0.45 mg/kg/day) was 16.25 (95% CI 5.360–49.253), the OR for platelet count $<19.5 \times 10^4$/μL was 4.40 (95% CI 1.969–9.840), the OR for lymphocyte count <1100/μL was 4.16 (95% CI 1.726–10.043), and the OR for IgG level <1050 mg/dL was 1.61 (95% CI 0.700–3.721), which suggested a strong association with the steroid dose (Table 2). For the underlying disease, the univariate analysis signified a corresponding involvement in DM/PM, but the multivariate analysis did not show a significant correlation. We also compared the antiviral treatment and nontreatment groups. As with the antigenemia analysis, daily steroid dose was the most significant treatment-related factor (Supplemental Table S2).

ROC curves were constructed for steroid dose, lymphocyte count, IgG level, and CMV antigenemia, which showed that the AUC of the steroid dose was the largest at 0.838 (95% CI 0.781–0.882); this implied a strong association between steroid dose and CMV antigenemia (Fig. 2).

4. Discussion

A retrospective observational study was conducted to examine the associated factors and the time of the onset of CMV antigenemia in patients with rheumatic diseases. To the best of our knowledge, this is the largest observational study in terms of the number of cases. The findings alluded that steroid dose was the most important factor associated with CMV antigenemia in patients with rheumatic diseases. A high dose of glucocorticoids has been reported to be a risk factor for CMV disease in patients with rheumatic diseases [25], which is consistent with the results of this study.

Of the patients with rheumatic diseases included in this study, 33.7% presented with CMV antigenemia. Previous reports have shown that the frequency of CMV antigenemia varies widely from 3% to 40% [15,17–21,24,26]. This difference was attributed to the type of the underlying rheumatic disease. Similarly, in the present study, the crude OR was different for each disease. However, in the multivariate analysis, these differences were not significant, and the steroid dose was found to be the strongest related factor. The risk was suggested to be due to the need for a high steroid dose, not to the disease itself.

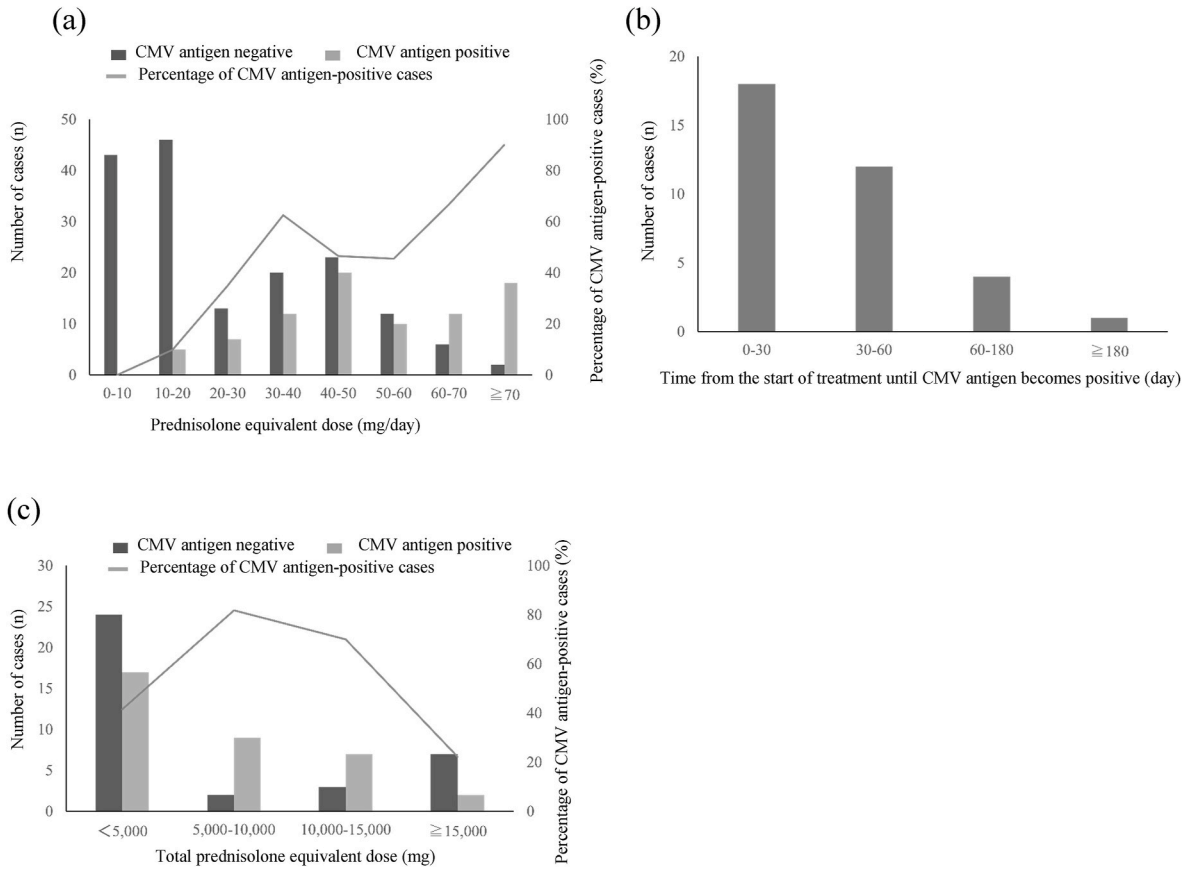


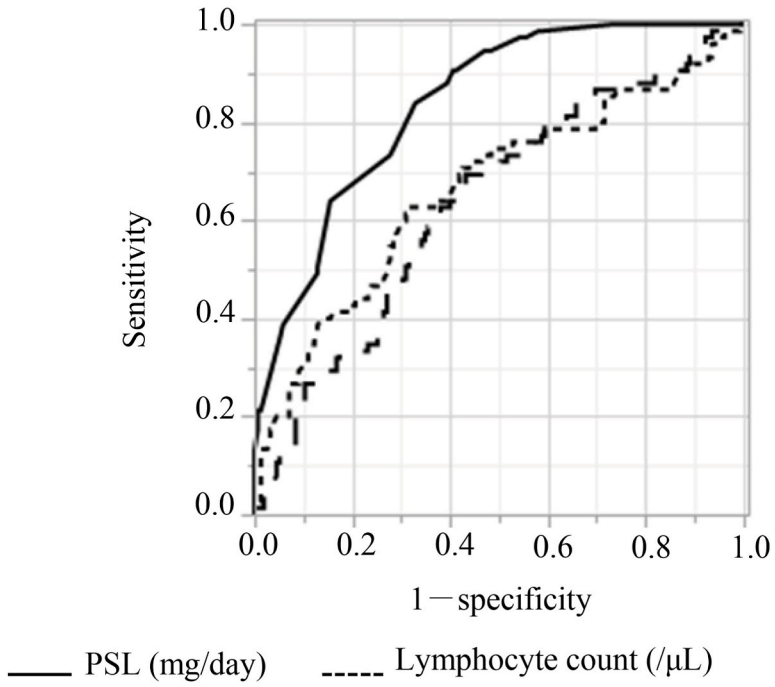
Fig. 1. (a) Daily steroid dose and cytomegalovirus (CMV) antigenemia. The Cochrane–Armitage trend test for CMV antigenemia and daily steroid dose (mg/day) showed a positive correlation ($p < 0.0001$). (b) The number of days from treatment initiation until the CMV antigen becomes positive. The median number of days from the initiation of immunosuppressive therapy until the CMV antigen became positive in patients with rheumatic diseases was 30 (interquartile range, 21–44) days, with 18 (51.4%) patients within 30 days and with 30 (85.7%) within 60 days. (c) Total steroid dose and CMV antigenemia. The Cochran–Armitage trend test for CMV antigenemia and total steroid dose showed no positive correlation ($p = 0.9292$).

Table 2
Univariate and multivariate analyses (CMV antigenemia).

	Univariate analysis			Multivariate analysis		
	cOR	95% CI	p value	aOR	95% CI	p value
Prednisolone dose ≥0.45 (mg/kg/day)	11.38	5.484–23.635	<0.0001	16.25	5.360–49.253	<0.0001
Albumin <3.0 (mg/dL)	1.36	0.787–2.344	0.2731	1.66	0.623–4.417	0.3109
LDH ≥250 (U/L)	3.25	1.882–5.614	<0.0001	2.65	1.170–6.012	0.0195
Lymphocyte count <1100 (/μL)	3.51	2.028–6.089	<0.0001	4.16	1.726–10.043	0.0015
Platelet count <19.5 (× 10^4/μL)	6.91	3.853–12.398	<0.0001	4.40	1.969–9.840	0.0003
IgG <1050 (mg/dL)	2.79	1.563–4.985	0.0004	1.61	0.700–3.721	0.2610
CRP <0.5 (mg/dL)	2.68	1.537–4.662	0.0004	2.14	0.773–5.914	0.1430
Steroid pulse therapy	4.45	2.465–8.027	<0.0001	0.81	0.315–2.095	0.6671
Diabetes mellitus	1.95	1.085–3.518	0.0256	1.42	0.568–3.572	0.4509
Dermatomyositis/polymyositis	3.29	1.452–7.472	0.0043	1.85	0.506–6.789	0.3513

cOR, crude odds ratio; aOR, adjusted odds ratio; CI, confidence interval; LDH, lactate dehydrogenase; CRP, C-reactive protein.

Regarding steroid doses, whether the cumulative dose or current dose is more important is often debated. The incidence of infections was significantly higher in the steroid-treated group than in the non-steroid-treated group when the cumulative dose of prednisolone equivalent was ≥700 mg [27], and the total steroid dose is generally considered a risk factor for infections. However, in this study, no significant association was found between CMV antigenemia and total steroid dose. A study reported that short-term steroid administration is associated with the risk of sepsis [28], which suggests that the daily steroid dose may be more important than the total steroid dose as a risk factor of infection. Furthermore, as for the time of the onset of CMV antigenemia in patients with rheumatic diseases, Sekiguchi et al. reported that the mean number of days from treatment initiation to CMV reactivation in patients with dermatomyositis was 6.1 ± 0.5 weeks (mean ± standard deviation) [29]. Moreover, Yamashita et al. reported that CMV antigen becomes positive within 60 days after treatment initiation in 13 of 14 patients (92.9%) [26]. The results of this study were similar to those of previous studies, which indicate that CMV reactivation is highly likely to occur within 2 months from the start of treatment in patients with rheumatic diseases. In patients with RA aged ≥65 years, current and recent glucocorticoid doses have been reported to be the greatest risk factors for severe infections [30]. This finding signifies that steroid administered 1–2 months prior to the onset of severe infections may be an extremely important predictor of infections.



	AUC	95% CI
PSL (mg/day)	0.8375	0.7805-0.8819
Lymphocyte count (/μL)	0.6640	0.5812-0.7379
IgG level (mg/dL)	0.6337	0.5544-0.7064

P < 0.0001

Fig. 2. Receiver operating characteristic analysis was performed to evaluate the association of cytomegalovirus antigenemia with the daily steroid dose, lymphocyte count, and IgG level. The area under the curve (AUC) was 0.838 [95% confidence interval (CI) 0.781–0.882] for the prednisolone (PSL) dose, 0.664 (95% CI 0.581–0.738) for the lymphocyte count, and 0.634 (95% CI 0.554–0.706) for the IgG level ($p < 0.0001$).

These results suggest that appropriate monitoring of CMV antigen based on the steroid dose is beneficial for at least 2 months after commencing treatment. In this multivariate analysis, prednisolone equivalent dose of 0.45 mg/kg/day is also a convincing value in the light of clinical practice. In the current management, IgG level is regularly monitored as an indicator of CMV reactivation, and immunoglobulin therapy may be considered when IgG levels are low [31]; however, the results of the present study did not show any strong association between CMV antigenemia and IgG level. Compared with IgG level and lymphocyte count used in actual clinical practice, steroid doses showed a significantly high AUC of 0.8375 in the ROC curve. This approach may avoid the development of CMV disease with a poor prognosis by considering preemptive therapy when CMV antigenemia is observed. Furthermore, immunosuppressive drugs were not strongly associated with CMV antigenemia in this study, implying the possibility that the concomitant use of immunosuppressive drugs in the initial treatment of rheumatic diseases and tapering of steroid doses as early as possible may reduce the risk of CMV reactivation.

In this study, biologics were used in 11 cases, and none of the patients had CMV antigenemia. Although there have been reports of CMV infection with biologics such as tumor necrosis factor blockade [32], information on biological therapy and CMV reactivation is limited [33]. The risk also varies greatly depending on the drug used. No patient in this study received rituximab or Janus kinase inhibitors, which have a wide range of effects. Because the number of cases is limited in this study, it is difficult to make a definitive judgment.

Lymphopenia, thrombocytopenia, and elevated LDH levels were observed in the group that developed CMV antigenemia. High-dose

steroids are considered a contributing factor to lymphocytopenia. The mechanism of glucocorticoid-induced lymphocyte depletion is thought to be that glucocorticoids inhibit lymphocyte differentiation involved in helper T cell type 1 immune responses by suppressing interleukin-12 secretion, and glucocorticoids above physiological doses induce T-cell apoptosis [34]. Possible mechanisms of CMV-induced thrombocytopenia include direct cytopathological effects, virus-induced haemophagocytosis, and immunological mechanisms [35]. LDH is not organ specific, but its levels are elevated in opportunistic infections, such as CMV pneumonia, pneumocystis pneumonia, and toxoplasma [36,37].

This study used antigenemia assay for detecting CMV. In Japan, the antigenemia assay is widely used for CMV monitoring; however, polymerase chain reaction (PCR) assay is the mainstream in other countries. The antigenemia assay is cost effective and can be used regardless of equipment or facility, whereas the PCR method is considered superior in terms of sensitivity. Several studies have shown that both methods are effective for detecting CMV infection [38]. Additionally, a positive correlation was found between the antigenemia assay and PCR assay [39]. Therefore, the present findings of associated factors could be considered in both assays.

This study has some limitations. First, as this was a single-center observational study, some bias in patient selection and results may not be ruled out. Second, the timing of CMV antigen measurement, selection of therapeutic agents, and drug doses were at the discretion of each attending physician and were not standardized. These points were unavoidable because of the retrospective nature of this study; however, we hope that prospective multicenter studies will be conducted in the future.

5. Conclusion

The findings of this study suggest that the daily dose of steroids is the most important factor associated with CMV antigenemia in patients with rheumatic diseases and that careful CMV monitoring during the first 2 months is highly important after initiating immunosuppressive therapy for the primary disease.

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Authorship statement

Conceived and designed the analysis: H. Ogata, N. Aoki, T. Koizumi, Y. Ohshima, S. Watanabe, H. Moro, T. Koya, and T. Kikuchi.

Data collection: H. Ogata, N. Aoki, K. Nagano, M. Hakamata, Y. Bamba, S. Shibata, and T. Koizumi.

Contributed data/analysis tools: H. Ogata, N. Aoki, and T. Koizumi.

Performed the analysis: H. Ogata, N. Aoki, and Y. Bamba.

Wrote the paper: H. Ogata, N. Aoki, and H. Moro.

Declaration of competing interest

T. Kikuchi reports receiving commercial research grants from the AstraZenica K. K., SHIONOGI & Co., Chugai Pharmaceutical Co., ONO PHARMACEUTICAL CO., and Eli Lilly Japan K. K. and reports receiving honoraria for lectures from AstraZeneca K. K. and Nippon Boehringer Ingelheim Co., Ltd.

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Appendix A. Supplementary data

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