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Incidence of Cytomegalovirus Antigenemia in patients with autoimmune rheumatic diseases: a 3-year retrospective study

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Abstract

Objective: To determine the incidence of positive CMV antigenemia (CMV-Ag) in patients with autoimmune rheumatic diseases (AIRD) and to describe the outcomes of these patients.

Methods: From January 2011 to December 2014, a total of 443 patients with AIRD were enrolled in this retrospective analysis. Demographic, clinical and laboratory data, current clinical manifestations, organs affected by CMV infection, therapeutic management and outcomes were evaluated. The CMV-Ag was considered positive when one cell was detected at least.

Results: CMV-Ag was requested in 70 (15.8%) patients with suspicious CMV infection and was positive in 24 (34.3%). The incidence rate of positive CMV-Ag was 4.97% (95% CI 3.1–7.4%). Systemic lupus erythematosus (SLE) (59%), followed by ANCA-related vasculitis (18.2%) and rheumatoid arthritis (9%) were the diseases more associated with positive CMV-Ag. At the time of CMV infection, SLE patients had moderate to severe disease activity, with high frequency of positive anti-dsDNA antibody (69.2%) and complement consumption (61.5%), as well as high doses of corticosteroids and use of immunosuppressants. The main CMV sites involved were lung (45.5%), bone marrow (40.9%) and gut (27.3%). Mortality rate was 45.5%, especially in those with higher doses of daily oral corticosteroids (107 ± 55.4 mg vs. 71.7 ± 46.3 mg; $p = 0.07$) and lower number of lymphocytes ($309 \pm 368.2/mm^3$ vs. $821 \pm 692.9/mm^3$; $p = 0.06$).

Conclusions: Our data showed high incidence of CMV-Ag in AIRD patients, particularly those with SLE and greater disease severity. In addition, it was observed high mortality in these patients, highlighting the CMV infection should be included in differential diagnosis.

Keywords: Cytomegalovirus, Infection, Antigenemia, Autoimmunity, Incidence

Introduction

Cytomegalovirus (CMV) is related to opportunistic infections in immunocompromised patients with autoimmune rheumatic diseases (AIRD) [1, 2]. Several studies have highlighted its pathogenic role in triggering or hampering some AIRD [3]. In immunocompromised individuals, the reactivation of latent CMV infection may cause fever, chills, weight loss, asthenia, hematological disorders (anemia, leukopenia, and thrombocytopenia) or severe symptomatic organ involvement, including hepatitis, chorioretinitis, encephalitis, pneumonitis and digestive hemorrhage [4].

The CMV antigenemia (CMV-Ag) is the main method for the diagnosis of infection due its high sensitivity (91%) and specificity (95%), as well as early and fast detection and therapeutic monitoring by number of affected cells [3]. On the other hand, it has some limitations, such as neutropenia below $1000/mm^3$ (false-negative) and other tests should be necessary for a better diagnosis [5, 6].

There are some epidemiological data and management guidance addressed to immunosuppressed patients, including AIDS and after solid organ and bone marrow transplantation [7–11]. However, there is a lack of evidence in patients with AIRD and the recommendations

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for managing these patients are extrapolated from transplantation data [12].

Thus, the aim of this study was to evaluate the incidence of CMV-Ag and describe the main outcomes over time in AIRD patients.

Patients and methods

Patients

Patients admitted to the rheumatology service at a tertiary university hospital in São Paulo/ SP, Brazil, from 01/JAN/2011 to 31/DEC/2014, were analyzed and those with clinical CMV suspicion infection and positive CMV-Ag for one cell, at least, were included. A total of 443 patients with AIRD were enrolled in this retrospective analysis. Patients with other viral infections, including hepatitis B and C, HIV, and Epstein-Barr were excluded. The positive CMV-Ag was defined when one cell was detected at least.

Clinical evaluation

Demographic, clinical and laboratory data were recorded for all patients. Specific details of each AIRD and current clinical manifestations, including disease activity, organs affected by CMV infection, therapeutic management (initial and secondary prophylaxis) and outcomes were also explored. For assessment of disease activity were used the *Systemic Lupus Erythematosus Disease Activiy Index* (SLEDAI) for SLE [13] and *Birmingham Vasculitis Activity Score* (BVAS) for ANCA associated vasculitis [14].

Laboratory evaluation of the CMV viremia

CMV-pp65 antigen detection was undertaken by the monoclonal antibody indirect immunofluorescence (IF) method (CMV Brite Turbo Kit, IQ Products, Gronigen, The Netherlands). The number of leukocytes stained positive every 200,000 neutrophils in peripheral blood was then documented.

Quantitation of CMV-DNA was undertaken by real-time fluorescence quantitative polymerase chain reaction (RT-PCR-fluorecence) technology (CMV nuclei acid quantitative assay kit, TaqMan® Roche – FAM, Branchburg, USA) when available. The criteria for positive result was CMV-DNA ≥ 500copies/ml. Viral inclusion bodies found in the tissue biopsy, stained with hematoxylin-eosin, were also considered positive for CMV infection.

Definition of CMV disease and follow-up protocol

Patients with laboratory abnormalities (anemia, leukopenia, thrombocytopenia or liver enzymes) or clinical manifestations, such as fever, gut or eye symptoms or lung injury, excluding other infection causes, were considered as suspicious symptomatic for CMV infection. CMV disease was defined when the confirmation had been performed by biopsy and identification of positive viral inclusion corpuscles or immunohistochemistry of affected organ.

After treatment with antivirals, patients had CMV-Ag repeated weekly until becoming negative. This outcome was defined as improvement of CMV infection.

Statistical analysis

All analyses were proceeded using SPSS 20.0 (*IBM, New York, USA*). Shapiro-Wilk or Kolmogorov-Smirnov tests were applied to assess the normality of the variables. To compare continuous variables, Student-t test or Mann-Whitney test were used. Pearson and Spearman correlation tests were used to analyse the correlation between variables. Categorical data were analyzed by chi-square test or Fisher's exact test. Significant variables in the univariate analysis or correlation tests were used for tailoring the multivariate regression models in which the positive CMV-Ag was considered as dependent variable and all other as independent, in order to explore main prognostic factors. Besides, ROC analysis was performed to determine the absolute cut-off value of the positive CMV-Ag related to death. *P* value below 0.05 was set as significant.

This study was approved by the Ethics and Research Committee of Hospital São Paulo / Unifesp (506.406).

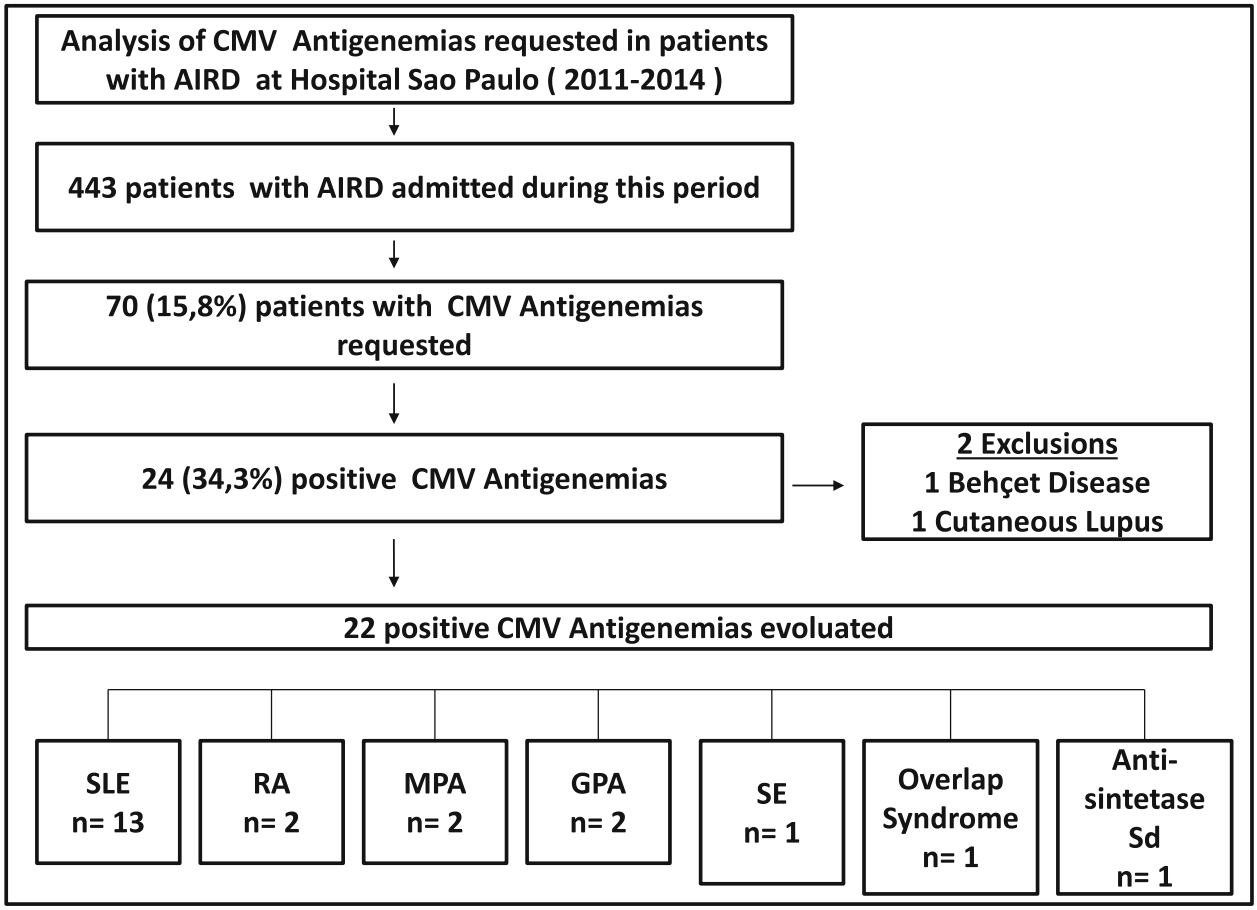
Results

From 443 patients with AIRD hospitalized in a tertiary university center, the CMV-Ag was requested to 70 (15.8%) patients with suspicious CMV infection and it was positive in 24 (34.3%).

Two positive CMV-Ag were excluded because one patient had cutaneous lupus (not systemic) and the other had Behcet's disease whose clinical manifestation of possible viral infection (acute diarrhea) was attributed later to adverse event by using of colchicine. Thus, 22 patients with AIRD and positive CMV-Ag were evaluated (Fig. 1). The incidence global rate of the positive CMV-Ag was 4.97% (95% CI 3.1 to 7.4%). Considering only lupus hospitalized patients, the CMV-Ag rate was 16.5% (95% CI 9.7 to 51.9%).

The main sites involved by CMV infection were lung, bone marrow and gut. Tables 1 and 2 show the main characteristics of AIRD patients with positive CMV-Ag. Lupus patients were younger than those with other AIRD (29.1 ± 13.4 years vs. 54.2 ± 21.1 years; $p = 0.03$). In addition, the majority of patients had high disease activity associated with severe infection, such as lupus patients (SLEDAI = 15.3 ± 9) and patients with ANCA-associated vasculitis (BVAS = 5.2 ± 3.8).

The length of hospital stay (11.5 ± 12 days) was long and there was a delay time between the beginning of symptoms and the CMV-Ag has been requested (7.8 ± 7.1 days). Besides, 16 (72.7%) patients had co-infections with other antimicrobial agents, such as *Candida albicans* and *Acinetobacter baumannii*, and there were five cases of polymicrobial infections.



CMV: cytomegalovirus. AIRD: autoimmune rheumatic diseases. SLE: systemic lupus erythematosus. RA: rheumatoid Arthritis. MPA: microscopic poliangiitis. GPA: granulomatosis with poliangiitis. SE: systemic sclerosis.

Fig. 1 Recruitment of positive CMV antigenemia for the study

Regarding the treatment for AIRD, 19 (86.4%) patients used corticosteroid (up to 1 mg/ kg/ day of prednisone or equivalent) and 11 (50%) patients used other immunosuppressants drugs during hospitalization, including cyclophosphamide.

Concerning the treatment for CMV, 15 (68.2%) of them received ganciclovir. In general, these patients tended to have more positive cells than those untreated [16 (1–500) vs. 1 (1–4); $p = 0.05$]. Only three patients reported adverse events related to ganciclovir, including cutaneous and cytopenia reaction.

Lupus patients had greater number of positive CMV-Ag than other AIRD. These patients were using high doses of corticosteroids and had received methylprednisolone pulse therapy in the last 6 months prior to infection. Moreover, the median time of disease was only 12 months (0–276), suggesting higher likely of viremia and CMV involvement in early disease. They had higher predominance of joint, kidney and hematological involvement, as well as higher positivity for anti-dsDNA antibody (69.2%) and complement consumption (61.5%). Few lupus patients had cutaneous or neurological involvement.

The mortality rate was 45.4% (10 deaths in total: 4 in SLE patients; 3 in patients with ANCA-associated vasculitis, 1 patient had systemic sclerosis, 1 with RA and other with overlap syndrome). Three deaths were observed between the seven patients who did not receive specific treatment for CMV, although not significant.

After assessing the risk factors for death, there was no difference among patients who survived or died regarding to age, average number of positive cells on antigenemia, site of virus involvement, hospitalization, symptoms until the first CMV-Ag be requested and pulse therapy in the last 6 months. However, there was a tendency to higher doses of oral corticosteroids (107 ± 55.4 mg/day vs. 71.7 ± 46.3 mg/ day; $p = 0.07$) and lower number of lymphocytes when patients who died were compared to those who survived (309 ± 368.2/ mm^3 vs. 821 ± 692.9/ mm^3; $p = 0.06$). Moreover, the surviving patients remained hospitalized for longer time than those who died (24.3 ± 23.9 days vs. 56.6 ± 35.1 days; $p = 0.017$) (Table 3).

Table 1 Clinical and laboratory data of 22 patients with autoimmune rheumatic disease (AIRD) and positive cytomegalovirus antigenemia

Patient	Age (years)/ Sex	AIRD	Immunosuppressive therapy in hospital	Lymphocyte Count (/μl)	Positive CMV antigenemia nuclei (/200.000PMN)	Sites involved by CMV infection	Symptoms	Outcome
1	67/F	SLE	CFA, PDN 130 mg/ day	1311	32	Gut	Esophageal ulcers	Death
2	34/F	SLE	AZA, CFA, PDN 80 mg/day	1356	1	Lung	Cough, dyspnea, fever	Improvement
3	17/F	SLE	PDN 200 mg/day	444	2	Cytopenia	Neutropenia, Thrombocytopenia	Improvement
4	22/F	SLE	PDN 60 mg/day	695	5	Gut	Mouth ulcers	Improvement
5	21/F	SLE	PDN 60 mg/day	135	500	Cytopenia / Lung	Trombocyotpenia, Cough, dyspnea, fever	Death
6	25/F	SLE	PDN 180 mg/day	525	1	Lung	Cough, dyspnea, fever	Death
7	16/F	SLE	MP + CFA, PDN 50 mg/day	850	108	Cytopenia	Febrile neutropenia	Improvement
8	20/F	SLE	MP + CFA, PDN 60 mg/day	792	1	Gut	Esophageal ulcers	Improvement
9	38/F	SLE	PDN 60 mg/day	2751	2	Lung	Cough, dyspnea, fever	Improvement
10	30/F	SLE	CFA, PDN 60 mg/ day	659	2	Cytopenia	Pancytopenia, fever	Death
11	25/F	SLE	MMF, MP, PDN 50 mg/day	853	164	Cytopenia	Anemia, Thrombocytopenia	Improvement
12	37/F	SLE	PDN 60 mg/day	80	46	Cytopenia /Gut	Anemia, diarrhea	Improvement
13	26/F	SLE	MP + CFA, PDN 90 mg/day	714	2	Lung	Cough, dyspnea	Improvement
14	77/F	SE	–	125	1	Cytopenia	Pancytopenia, fever	Death
15	29/M	Overlap Sd.	PDN160mg/day	246	16	Lung	Cough, dyspnea	Death
16	70/M	RA	MP, PDN 20 mg/day	77	1	Cytopenia	Pancytopenia, fever	Improvement
17	17/M	RA	PDN 160 mg/day	689	1	Lung	Cough, dyspnea	Death
18	42/F	MPA	PDN 100 mg/day	197	4	Lung	Cough, dyspnea, Fever	Death
19	77/F	MPA	PDN 100 mg/day	372	500	Cytopenia / Lung	Anemia, Leukopenia, Cough, Fever	Death
20	63/F	GPA	CFA, PDN 30 mg/ day	857	9	Gut	Gastric ulcer	Improvement
21	58/M	GPA	AZA, MP, PDN 120 mg/day	213	73	Gut	Gastric ulcer	Death
22	55/F	Anti-sintetase Sd.	CFA, PDN 100 mg/ day	975	7	Lung	Cough, dyspnea	Improvement

CMV cytomegalovirus, *SLE* Systemic Lupus Erythematosus, *SE* Systemic sclerosis, *Overlap syndrome* Systemic Lupus Erythematosus + Systemic sclerosis + polymyositis, *RA* rheumatoid arthritis, *MPA* microscopic polyangiitis, *GPA* granulomatosis with polyangiitis, *F* Female, *M*, Male, *AIRD* autoimmune rheumatic disease, *PDN* Prednisone, *AZA* Azathioprine, *MMF* mycophenolate mofetil, *CFA* Cyclophosphamide (pulse), *MP* Methylprednisolone (pulse), *MP* + *CFA* combined pulse: methylprednisolone and cyclophosphamide. a: Maximum dose during hospitalization. b: methylprednisolone pulse 1 g / day for 3 consecutive days

Table 2 Demographic and clinical data of 22 patients with autoimmune rheumatic disease (AIRD) and positive cytomegalovirus antigenemia

Female sex	19 (90%)
Age (years)[a]	39.4 ± 20.8
AIRD	
SLE	13 (59%)
ANCA-associated Vasculitis	4 (18.2%)
RA	2 (9%)
Systemic sclerosis	1 (4.5%)
Overlap syndrome	1 (4.5%)
Anti-sintetase syndrome	1 (4.5%)
Diagnosis AIRD[b] Time (months)	10.5 (0–276)
Hospitalization cause[a]	
Activity + Infection	11 (50%)
Infection only	8 (36.5%)
Activity only	3 (13.6%)
AIRD treatment	
Maximum dose of corticosteroids in hospital (mg/ day)[a]	87.7 ± 52.5
Corticosteroids dose above 1 mg /kg/ day[a]	19 (86.4%)
Methylprednisolone Pulse Therapy[a]	11 (50%)
Immunosuppressant medications[a]	11 (50%)
Site of CMV infection[a]	
Lung	10 (45.4%)
Cytopenia	9 (40.9%)
Gastrointestinal tract	6 (27.3%)
Hospitalization time[a](days)	41.9 ± 34.1
Hospitalization time until CMV-Ag be requested[a](days)	11.5 ± 12
Time of symptoms until CMV-Ag be requested[a](days)	7.8 ± 7.1
Time from the first positive CMV-Ag to specific treatment be started[a](days)	3.3 ± 3.1
Number of positive CMV-Ag nuclei after specific treatment	
With Ganciclovir[b]	15 (1–500)
No ganciclovir[b]	7 (1–4)
Co-Infections[a]	16 (72.7%)
Polymicrobial Infections	5 (22.7%)
CMV reactivation during hospitalization	0
Prophylaxis after standard Ganciclovir treatment	0

[a]Mean ± standard deviation; [b]Median (minimum and maximum); *AIRD* Autoimmune Rheumatic Diseases, *CMV-Ag* cytomegalovirus antigenemia, *SLE* Systemic Lupus Erythematosus, *RA* Rheumatoid Arthritis

Regarding absolute CMV-Ag, three (13.6%) patients had values above five cells and eight patients (36.4%) had values above 10 cells. However, none of these two cutoffs CMV-Ag had significant association with death or poor outcome.

Discussion

Our data showed high incidence of positive CMV-Ag in hospitalized patients with AIRD, as well as severe disease severity and poor prognosis, including death.

To our the best knowledge, this is the first study to highlight the incidence of positive CMV-Ag in hospitalized patients with severe AIRD, especially SLE and ANCA-associated vasculitis. Thus, it could not be compared with another retrospective studies no incidence data and heterogeneous prevalence (from 2 to 50%) [4, 8, 15, 16].

In addition to severity and high disease activity, it is worthy emphasizing that high doses of corticosteroids may have impaired the immune response in our patients [4, 17, 28]. Considering that over 95% of general

Table 3 Comparison of clinical and demographic characteristics of patients with positive cytomegalovirus antigenemia according to the outcome: survivor or death

	Death $n = 10$	Survivor $n = 11$	p
Age[b] (years)	44.3 ± 23.4	35.5 ± 18.3	0.32
Lymphocyte Count (/μL)[b]	447.2 ± 368.2	870.3 ± 692.9	0.06
CMV-Ag[b,c]	113 ± 205,2	29 ± 52.9	0.67
Oral glucocorticosteroids (mg/ day)[a,b]	107 ± 55.4	71.7 ± 46.3	0.07
Methylprednisolone Pulse Therapy, n			
Yes	3 (30%)	8 (72.2%)	0.19
No	7 (70%)	4 (36.6%)	
Hospitalization time[b]	24.3 ± 23.9	56.6 ± 35.1	0.017
Hospitalization time until CMV-Ag be requested (days)[b]	9.9 ± 14	12.9 ± 10.5	0.42
Time of symptoms until CMV-Ag be requested (days)[b]	7.9 ± 8.2	7.8 ± 6.4	0.77
Time from the first positive CMV-Ag to specific treatment be started (days) [b]	3.4 ± 2.6	3.3 ± 3.7	0.54
CMV suspicious cause, n			
Cytopenia	2 (20%)	4 (36.4%)	
Cytopenia e GIT	0 (0)	1 (9.1%)	
GIT	2 (20%)	3 (27.3%)	0.59
Pneumonia	4 (40%)	4 (36.3%)	
Cytopenia e Pneumonia	2 (20%)	0 (0)	

CMV-Ag: cytomegalovirus antigenemia, *b* mean ± standard deviation, *c* cels / 200.000polimorphonuclear. [a]Maximum corticosteroid dose during hospitalization. *GIT* gastrointestinal tract. Cutoff value of 10 positive cores for CMV antigenemia

population have immunological memory for CMV, likely these three aspects together could be involved for reactivation of latent viral infection [4, 12, 17, 18]. On the other hand, other authors found no association between CMV infection and immunosuppressive medications, especially corticosteroids [3, 8, 16].

The lung (45.5%) was the organ with the highest suspect involvement by CMV infection in our patients, confirming that the viral reactivation data in tracheal aspirates from immunosuppressed patients must be the main pathophysiologic mechanism, as well as pneumonitis reports and respiratory failure [21, 22]. However, it is important to state the possibility of pneumonia caused by multiple microbial agents. Cytopenia had the second place in frequency (40.9%), unlike recent retrospective report of 105 patients with SLE and active CMV infection related 81% of patients with some cytopenia [23]. The simultaneous involvement of various organs can also occur in immunosuppressed patients and was observed in 3 (13.6%) of our patients. Although the presence of cytopenia may constitute a simple and early warning for CMV infection in immunocompromised patients with AIRD, this finding was not specific, since it can also mean disease activity and toxicity to immunosuppressants.

Several mechanisms may explain the role of CMV and the onset of rheumatic disease or as a possible trigger, as well as its association with increased mortality in lupus patients [23]. Due to their broad cell tropism, CMV has great variety of clinical manifestations in immunocompromised patients and can even be confused with the disease activity [3, 12, 19, 23, 25]. At diagnosis of CMV infection, SLE patients had higher incidence of hematologic, joint and kidney activity. Unlike cytopenias, articular and kidney involvement did not usually occur in reactivation of CMV infection and may be useful for the differential diagnosis between both clinical scenarios (infection vs. disease activity) [23].

Tasai et al. (2012) showed SLE patients infected by CMV had higher scores of SLEDAI, poor prognosis and increased mortality [12]. Our data confirm these interesting epidemiological features, since more than half of patients with positive CMV-Ag had SLE, particularly with early-onset disease and were youth. Thus, these findings address the role of CMV as trigger, as well as by collaborating on innate immunity and dysfunction of humoral and cellular immune response [4, 15, 24, 26, 27].

The diagnosis of CMV infection is not performed routinely by rheumatologists and there is no active search or specific treatment for patients with AIRD. Our study provides a new information about modern strategies headed for these patients. First of all, it is an alert to the presence of infection or co-infection with CMV, according to our high incidence of CMV-Ag in the first 10 days of hospitalization. Secondly, the red flag is the fast and sensible methodology for detecting suspicious cases of CMV infection in AIRD patients. Thirdly, the delay for

requesting CMV-Ag and the risk of severe disease severity and higher mortality rate.

There are well-established recommendations for screening, treatment and prevention of CMV infection in immunocompromised patients with other conditions, such as cancer, AIDS and transplants [5, 7–11, 20]. However, there are a lack of information about management of AIRD patients, highlighting the relevance of current study and supporting the necessity for the development of specific protocols in this scenario.

In 2008, Takizawa et al. suggested the cut-off of 11.2 cells/ 200,000/ neutrophils as a significant value for distinguishing symptomatic and asymptomatic infections as well as higher positive predictive value for CMV infection and mortality in patients with AIRD [16]. As there is no consensus about the significant number of cells for AIRD patients, we considered at least one cell for the first investigation associated to clinical findings (fever plus cytopenias and/ or pulmonary infiltrates and/ or gut lesions and/ or hepatitis). However, in further re-analyses with several cut-off points, including 5 and 10 cells, we did not also find a significant CMV-Ag cut-off. Thus, our data confirm that, regardless age, duration of symptoms, number of positive cells, viral involvement site, the simple presence of CMV-Ag was associated with severe illness and higher risk of death, especially in those with shorter hospital stay and higher dose of corticosteroids.

Considering that AIRD hospitalized patients have multiple and complicated medical conditions, such as systemic inflammation, co-infections and renal failure, it is very difficult to assure the real direct cause of death and the multifactorial aspects altogether may occur among themselves.

Nonetheless, our study has some limitations. Firstly, it is related to CMV-Ag definition itself, because we cannot be sure that the presence of only one positive cell could be indicative of CMV infection. Secondly, is related to sample size, lack of control group and the heterogeneity of autoimmune diseases. Thirdly, we should not generalize our findings for outpatient patients or systematically request CMV-Ag for all hospitalized patients without a clinical suspicion. In addition, it is important to state that in any suspected case is need to confirm the CMV disease by histopathological analysis, for instance.

Although the survival patients with DRAI have kept imunossupression, none of them reactivated CMV over time (mean follow-up time 2 years), even without receiving prophylactic treatment with ganciclovir as suggested by protocols for transplanted patients. These new data emphasize that specific protocols are necessary for establishing appropriate diagnosis, treatment and monitoring CMV status in patients with AIRD, including prospective randomized controlled trials.

Conclusions

Our data showed high incidence of CMV-Ag in AIRD hospitalized patients, particularly early-onset lupus, severe disease activity, and higher mortality. Thus, the possibility of CMV infection should be included in differential diagnosis in AIRD patients.

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Availability of data and materials
The data of this article can be found at Rheumatology Division of Universidade Federal de São Paulo / Unifesp.

Author's contributions
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Ethics approval and consent to participate
The study was approved by the Ethics and Research Committee of Hospital São Paulo / Unifesp (number 506.406).

Consent for publication
All the patients signed the informed consent form.

Competing interests
The authors declare that they have no competing interests.

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