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Reactivation of latent cytomegalovirus infection in patients with rheumatologic disease: a case–control study

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Abstract

The disease burden, risk factors and clinical sequelae of CMV reactivation in patients with rheumatologic conditions is poorly understood. We have described a cohort with underlying rheumatic disease and CMV, and compared a subgroup with systemic lupus erythematosus (SLE) to controls to identify potential risk factors for CMV reactivation. Adults with rheumatic disease and CMV infection from 2000–2015 were identified. SLE cases were matched 3:1 with controls based on age, sex and year of admission, and compared. Fourteen patients were included (6 SLE, 4 rheumatoid arthritis, 2 sarcoidosis, 1 psoriatic arthritis, 1 microscopic polyangiitis). Seven had viremia alone, the remainder tissue-invasive disease. Thirteen received glucocorticoids prior to CMV reactivation. Fever was the most common symptom, and coinfections were seen in eight including four with bacteremia. Thirteen received antiviral therapy (median 33 days), four died during hospitalization. Six patients with underlying SLE and CMV reactivation were compared to 18 SLE controls. Cases received more glucocorticoids prior to admission (median 36.5 vs. 2.5 mg/day, $p=0.006$), had longer hospitalizations (median 47 vs. 7 days, $p=0.006$) and more coinfections (67% vs. 17%, $p=0.04$). There were no significant differences in symptoms at presentation. CMV reactivation occurs in patients with rheumatologic disease, can result in severe clinical sequelae, and is difficult to distinguish from a flare of the underlying disease. Patients with CMV received higher doses of glucocorticoids and developed more co-infections. CMV should be considered during the evaluation of a febrile illness in this complex patient population.

Keywords Cytomegalovirus · Rheumatic disease · Systemic lupus erythematosus

Background

Cytomegalovirus is a common β-herpesvirus that establishes life-long latency following primary infection. In healthy individuals, continuous immune surveillance prevents viral replication but reactivation can occur with immunosuppression [1, 2]. This is best described in patients with HIV-AIDS and transplant recipients, where clinical sequelae can range from a mild febrile illness to severe end-organ disease and treatment protocols are well established [2–4]. More recently, CMV reactivation has been recognized as a cause of disease in other patient populations, such as those with underlying rheumatic disease [5–8]. Treatment for these conditions often involves the use of potent immunosuppressive agents and prolonged courses of high dose glucocorticoids, increasing the risk of opportunistic infections including CMV [9, 10]. Additionally, the underlying disease process itself is often associated with a degree of immune dysfunction. Though less well characterized, the spectrum of CMV disease seen in these patient groups appears to be similar

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to the transplant populations, ranging from asymptomatic viremia to severe systemic and gastrointestinal tract disease requiring prolonged antiviral therapy [11, 5–8]. Coinfections with other typical and opportunistic pathogens appear to be common and associated with a higher mortality [12]. One of the largest published studies to date is a retrospective cohort of 7377 patients with underlying rheumatologic disease, of whom 151 (2%) developed CMV disease [6]. One hundred seventeen (77%) of the CMV-positive patients were symptomatic, and 44 (29%) died. Eighty-four patients were treated with ganciclovir, but there did not appear to be a significant treatment benefit. Lymphopenia and the presence of symptoms were independent risk factors for mortality [6].

Within the rheumatic disease population, CMV has been best characterized in patients with systemic lupus erythematosus (SLE) [13]. This group is at particularly high risk of CMV reactivation, which can cause significant illness and can be difficult to clinically distinguish from an SLE flare [14, 15]. There are some reports suggesting that CMV may have a role in triggering new-onset SLE [16, 17]. In a study of 40 cases of CMV reactivation in patients with biopsy-proven lupus nephritis, 17 (46%) were symptomatic and coinfections were seen in 15 (38%). Treatment benefit with ganciclovir was observed in symptomatic patients but not in those with asymptomatic viremia [7].

While some patterns are emerging from these reports, the full spectrum of CMV disease, risk factors for reactivation, and long-term clinical implications are not well understood in this patient population. Many prior studies have significant methodological limitations and were based on older diagnostic techniques such as the pp65 antigen rather than PCR-based CMV viral load testing [18–20]. An improved understanding of CMV disease in the rheumatologic population is important to inform the role of virologic surveillance, prophylaxis, and antiviral therapy. As such, the aim of this study was to describe a retrospective cohort of patients with underlying rheumatologic disease and CMV reactivation, and to compare a subset of patients with SLE to matched controls to explore potential risk factors for CMV reactivation and impact on outcomes.

Methods

Study design, case identification and data collection

This retrospective case–control study was conducted at Tufts Medical Center, a 415-bed academic medical center in Boston, MA, USA. The Tufts Medical Center institutional review board approved this study (approval number 12618) and informed consent was not required given its retrospective nature and minimal risk.

Cases were identified by searching for patients over the age of 18 years with positive test results for CMV (including viral cultures, histopathology, and viral load testing) and an underlying diagnosis of an inflammatory/autoimmune rheumatic disease from 2000–2015. Transplant recipients, patients with HIV, hematologic malignancy or other conditions requiring concomitant immunosuppressive therapy, those with non-inflammatory rheumatic conditions such as osteoarthritis or gout, cases of primary CMV infection, and those lost to follow-up were excluded. In order to capture cases where CMV likely had a significant contribution to the overall disease state, patients were also excluded if they had a single low-positive viral load (e.g. <1000 copies/mL) or positive viral culture that resolved spontaneously and did not require antiviral therapy.

Clinical and laboratory data were obtained from medical records. Symptoms were recorded at both time of admission and CMV diagnosis. Laboratory results were obtained from the day of admission, CMV reactivation, and discharge. When data were not available for the same day, values within 4 days were used. For the SLE cases and controls, anti-dsDNA and complement levels (C3 and C4) within 3 weeks of admission were recorded. Microbiology records were reviewed for the presence of co-infections within 1 month before or after the index admission including bloodstream infections, *Clostridium difficile*, invasive fungal infections and reactivation of other herpesviruses.

Immunosuppression

Immunosuppressive treatment history for the underlying rheumatic disease was obtained, including drug, dose, and timing of administration prior to and during index admission. Glucocorticoids were converted to prednisone-equivalents and average daily doses were calculated to allow for easier comparison between patients. Regimens were classified as low dose (≤ 7.5 mg/day), medium dose (>7.5 but ≤ 30 mg/day), high dose (>30 but ≤ 100 mg/day), and very high dose (>100 mg/day). Glucocorticoid regimens were also categorized as maintenance (long-term lower dose regimens typically prednisone 5–10 mg/day), taper (shorter, higher intensity courses weaned down over a period of days to weeks), and/or pulse-dose (≥ 250 mg/day for one or a few days), with the maximum dose received during each course recorded. The number of steroid pulses during these time periods was also recorded [21]. Steroid-sparing immunosuppressive drugs included biologic agents (e.g. rituximab, etanercept) and other disease-modifying drugs (e.g. cyclophosphamide, methotrexate). For the agents dosed less frequently than once daily, we considered the patient to be receiving the treatment if the length of time between last dose and admission date was less than the previously reported time interval between doses.

Control selection

Patients with SLE, the largest subgroup, were matched 3:1 with control patients. Potential controls were identified by searching electronic medical records by International Classification of Disease Ninth Edition (ICD-9) [22] code for patients with SLE admitted for a flare of their disease but without evidence of CMV reactivation, then matched to cases based on age (within 8 years) and year of admission (as close as possible but no more than 8 years before or after). The same exclusion criteria were applied to controls as for cases; patients known to be CMV antibody negative were also excluded.

CMV diagnosis and treatment

Viral load, viral culture and histopathologic testing were performed using standard techniques. Over the study period, three different viral load assays were used: (1) the Hybrid Capture CMV DNA assay (version 2.0), Digene Corp™, Silver Spring, MD, USA (now Qiagen), a whole blood assay with a detection range of 2.1 to > 830 pg/mL (1997–2008); (2) a whole blood assay performed by Quest Diagnostics (Chantilly, VA, USA) with a range of detection of 200 to > 200,000 copies/mL (2008–2011); and (3) a plasma viral load assay (Focus Diagnostics™ "Simplexa" kit) with a range of detection of 1000 (values below 1000 can be detected but not quantified) to 500,000 copies/mL (2011–2015). Invasive procedures (e.g. gastroscopy, colonoscopy, bronchoscopy) were performed as clinically indicated to obtain tissue samples for additional testing. Tissue or cytology specimens were examined for the presence of characteristic CMV inclusion bodies with hematoxylin and eosin staining. Immunohistochemical stains using CMV-specific mouse monoclonal antibodies (Cell Marque, Sigma-Aldrich, Rocklin, CA, USA) were performed on request or clinical suspicion. Blood buffy coat, tissue, urine and bronchoalveolar lavage samples were cultured using the rapid shell-vial technique and conventional viral culture using human fibroblast cell lines, with CMV detection by direct immunofluorescence using conjugated monoclonal antibodies against CMV immediate early antigen 1 and 2 (Light Diagnostics™, EMD Millipore Corporation, Temecula, CA, USA). CMV end-organ disease required laboratory confirmation of CMV plus clinical evidence of organ dysfunction.

Standard treatment of CMV infection was with intravenous ganciclovir 5 mg/kg twice daily or oral valganciclovir 900 mg twice daily with doses adjusted for renal impairment according to the package insert [23, 24]. Throughout the study period, there were no recommendations or protocols in place for routine screening of this patient group with either viral load or antibody, no prophylaxis was used, and all patient management (such as duration of therapy and frequency of viral load monitoring following treatment completion) was at the discretion of the individual treating clinicians.

Statistical analysis

Basic descriptive statistics were calculated, with categorical data reported as counts and percentages, continuous data as mean ± standard deviations if normally distributed and medians with ranges if non-normally distributed. Missing data for the variables of interest were negligible. We initially planned to perform a paired analysis using conditional logistic regression, however given the small sample size, this was not possible for all variables. As such, we treated the two groups independently and performed the Chi-square/Fishers' exact test for categorical variables, Student's *t* test for normally distributed variables, and Wilcoxon rank sum test for non-normally distributed continuous variables. p values < 0.05 were considered statistically significant. All analyses were performed with the R statistical software platform version 3.4.1 (RStudio version 1.0.153).

Results

Patient characteristics

Twenty-four patients with rheumatic disease and positive CMV testing were initially identified, however ten were excluded (7 with asymptomatic low-level viremia, 1 with a failing kidney transplant, 1 patient with comorbid inflammatory bowel disease, and 1 lost to follow-up before treatment could be instituted). Individual details of the 14 patients in our final cohort are shown in Table 1. Mean age was 54 ± 19.5 years, 12 (86%) were female and SLE was the most common underlying diagnosis. All patients had received some form of treatment for their rheumatic disease within 3 months of CMV reactivation date, with 13 (93%) receiving glucocorticoids, 9 (64%) receiving a non-biologic steroid-sparing agent, and 2 (14%) receiving a biologic agent. Eight (57%) patients were on maintenance glucocorticoids, and 10 (71%) received a tapering course during the preceding 3 months. The median average daily dose of glucocorticoids during the 3 months preceding CMV reactivation date was 25 mg (range 6–100 mg). The most common symptoms at time of CMV reactivation were fever (86%) and fatigue (71%). Gastrointestinal symptoms, including nausea, vomiting, and decreased appetite were also common, affecting 64% of patients. Thrombocytopenia and/or leukopenia were present in 8/14 (57%). Overall patient characteristics are further summarized in Table 2.

Table 1 Description of clinical characteristics of individual patients with rheumatologic disease and CMV reactivation

Age/sex	Rheumatologic diagnosis	Immunosuppression[a]	Symptoms at CMV onset	Peak viral load	LOS (days)	Antiviral therapy[b]	Co-infections	Outcome
38/F	SLE, lupus nephritis	Medium-dose maintenance prednisone, pulse IV methylprednisolone, mycophenolic acid	Fever, diarrhea, anemia	491.1[d]	8	3 days IV, 66 days oral[c]	Non-typhoidal *Salmonella* gastroenteritis	CMV relapses at 2 months, 29 months Alive: 77 months
36/F	SLE, lupus nephritis, myocarditis	Low-dose maintenance prednisone, high-dose IV hydrocortisone taper	Fever, abdominal pain, nausea, vomiting, decreased appetite, thrombocytopenia	NP	84	34 days IV, 51 days oral	MRSA and *Enterobacter cloacae* bacteremia, *Clostridium difficile*	Alive: 154 months
18/F	SLE, lupus nephritis	Medium-dose maintenance prednisone, pulse IV methylprednisolone	Fever, malaise, abdominal pain, nausea, vomiting, diarrhea, hepatitis, anemia	18.2[d]	31	16 days IV, 1 dose CMVIG	*Streptococcus viridans* coagulase negative *Staphylococcus* bacteremia	Relapse: 15 days Alive: 18 months
64/F	SLE, CNS vasculitis	Low-dose maintenance prednisone, high-dose IV hydrocortisone taper, hydroxychloroquine	Fever, respiratory distress, abdominal pain, nausea, vomiting, pneumonia, anemia, thrombocytopenia	329[d]	86	38 days IV, 132 days oral, 8 doses CMVIG	None	Alive: 79 months
30/F	SLE, lupus nephritis, pericarditis, pleural effusion	High-dose methylprednisolone taper, mycophenolic acid	Fever, cough, abdominal pain, nausea, diarrhea, anemia	1320[e]	9	27 days IV, > 5 days oral	None	LTFU: 1 month
39/F	SLE, pericarditis, lupus cerebritis	High-dose prednisone taper, pulse IV methylprednisolone, hydroxychloroquine, rituximab	Fever, malaise, productive cough, anemia	16,142[f]	62	13 days IV	Pulmonary *Mycobacterium tuberculosis, Clostridium difficile, Pseudomonas aeruginosa* bacteremia	Deceased: 46 days
63/F	RA	Low-dose maintenance prednisone, medium-dose prednisone taper, hydroxychloroquine	Fever, malaise, cough, weight loss, diarrhea	31.5[d]	9	5 days IV, 47 days oral	None	Relapse: 18 months, 24 months Alive: 85 months
79/F	RA	High-dose IV hydrocortisone, leflunomide	Malaise, decreased appetite, thrombocytopenia, hepatitis	275,152[e]	28	6 days IV, 36 days oral	Pulmonary/chest wall *Mycobacterium tuberculosis*	Deceased: 53 months
81/F	RA	Low-dose maintenance prednisone, high-dose prednisone taper, hydroxychloroquine, leflunomide	Malaise, abdominal pain, hepatitis	13,987[e]	11	30 days IV, 29 days oral	None	Deceased: 55 months

Table 1 (continued)

Age/sex	Rheumatologic diagnosis	Immunosuppression[a]	Symptoms at CMV onset	Peak viral load	LOS (days)	Antiviral therapy[b]	Co-infections	Outcome
66/M	RA	Medium-dose maintenance prednisone, high-dose prednisone taper	Fever, malaise, pneumonia, anemia	NP	54	None	Intra-abdominal *Candida glabrata* *Clostridium difficile*	Deceased: 10 days
63/F	Sarcoidosis	Low-dose maintenance prednisone, high-dose IV methylprednisolone	Fever, malaise, abdominal pain, nausea, decreased appetite, diarrhea, thrombocytopenia	158.3[d]	23	14 days IV	*Staphylococcus aureus* empyema	Deceased: 17 days
75/M	Sarcoidosis	High dose prednisone taper, very high-dose IV methylprednisolone	Fever, encephalopathy, abdominal pain, vomiting, anemia, thrombocytopenia	431,121[f]	29	11 days oral, 10 days IV	None	Deceased: 22 days
46/F	Psoriatic arthritis	Etanercept	Fever, malaise, thrombocytopenia	7874[e]	n/a	19 days oral	None	LTFU: 2 months
58/F	Microscopic polyangiitis, cresenteric glomerulonephritis	High-dose prednisone taper, pulse IV methylprednisolone, cyclophosphamide	Fever, malaise, weight loss, abdominal pain, poor appetite, diarrhea, hepatitis, anemia, thrombocytopenia	> 500,000[f]	28	27 days IV, 79 days oral, 1 dose CMVIG	*Enterococcus faecalis, Klebsiella pneumoniae* bacteremia	Alive: 61 months

CMV cytomegalovirus, *LOS* length of stay, *SLE* systemic lupus erythematosus, *RA* rheumatoid arthritis, *IV* intravenous, *CMV IG* CMV immune globulin, *NP* not performed, *LTFU* lost to follow up

[a]Within 3 months of CMV diagnosis. Glucocorticoid dosing categorized as low dose (≤7.5 mg/day), medium dose (> 7.5 but ≤ 30 mg/day), high dose (> 30 but ≤ 100 mg/day), and very high dose (> 100 mg/day), and pulse dose (≥250 mg/day for one or a few days) [21]

[b]Antiviral therapy was with IV ganciclovir and oral valganciclovir

[c]This patient relapsed 62 days following treatment, while receiving prophylactic dose valganciclovir, prompting re-initiation of treatment dose IV ganciclovir

[d]Assay 1 (whole blood, pg/mL). [e]Assay 2 (whole blood, copies/mL). [f]Assay 3 (plasma, copies/mL). Refer to methods for further details of viral load assays

Table 2 Baseline characteristics of the overall cohort of patients with rheumatologic disease and CMV reactivation ($n=14$)

Characteristics	Details ($n=14$)
Demographics	
Female sex, no. (%)	12 (86%)
Age at admission (years), mean ± SD	54 ± 19.5
Race, no. (%)	
White	6 (43%)
Asian	5 (36%)
Hispanic	2 (14%)
Black	1 (7%)
Current smoker, no. (%)	1 (7%)
Dialysis prior to CMV onset, no. (%)	3 (21%)
HIV seronegative (vs. not tested), no. (%)	8 (57%)
CMV seropositive (vs. not tested), no. (%)	9 (64%)
Rheumatic disease history	
Underlying disease, no. (%)	
SLE	6 (43%)
Rheumatoid arthritis	4 (29%)
Sarcoidosis	2 (14%)
Psoriatic arthritis	1 (7%)
Microscopic polyangiitis	1 (7%)
Total number of admissions within previous year, median, range	1, 0–5
Years of rheumatologic disease prior to CMV, median, range	7, 0.2–46.4
Immunosuppression within 3 months prior to CMV	
Any glucocorticoids, no. (%)	13 (93%)
Maintenance prednisone, no. (%)	8 (57%)
Dose (mg), mean ± SD	8 ± 5
Received taper, no. (%)	10 (71%)
> 30 mg/day, no. (%)	7 (50%)
Maximum dose within 1 month of CMV (mg), mean ± SD	39 ± 19
Maximum dose within 3 months of CMV (mg), mean ± SD	46 ± 23
Any IV glucocorticoids, no. (%)	8 (57%)
Pulse dose IV glucocorticoids, no. (%)	4 (29%)
Average daily dose, prednisone equivalent, median, range ($n=13$)	25, 6–100
Biologic agent, no. (%)	
Etanercept	1 (7%)
Rituximab	1 (7%)
Other immunosuppression, no. (%)	
Hydroxychloroquine	4 (29%)
Mycophenolate	2 (14%)
Leflunomide	2 (14%)
Cyclophosphamide	1 (7%)
CMV clinical information	
Duration of symptoms prior to CMV (days), median, range	32, 7–90
Symptoms at time of CMV diagnosis, no. (%)	
Fever	12 (86%)
Fatigue	10 (71%)
Nausea, decreased appetite	9 (64%)
Abdominal pain	8 (57%)
Myelosuppression	8 (57%)
Diarrhea	6 (43%)
Pneumonia	5 (36%)
Hepatitis	5 (36%)

Table 2 (continued)

Characteristics	Details ($n=14$)
Admitted for CMV, no. (%)	13 (93%)
Reason for admission ($n=13$), no. (%)	
Rheumatic disease flare	5 (36%)
CMV	4 (29%)
Other	4 (29%)
Year of admission, median, range	2008, 2000–2013
Length of stay (days), median, range	28, 8–86
Admitted to ICU, no. (%)	9 (69%)
Days from admission to CMV diagnosis, median, range	7, 0–44
Viremia, no. (%)	12 (86%)
Peak viral load, median, range[a]	
Assay #1 (pg/mL, $n=5$)	158.3, 18.2–491.1
Assay #2 (copies/mL, $n=4$)	10,931, 1,320–275,152
Assay #3 (copies/mL, $n=3$)	431,121, 16,142–500,000
Confirmed non-blood site, no. (%)	
Gastrointestinal	4 (29%)
Pulmonary	3 (21%)
Antiviral therapy, no. (%)	
IV only	2 (14%)
IV and oral	9 (64%)
Oral only	2 (14%)
Treatment duration (days), median, range	33, 13–171
Adjunctive CMV immune globulin, no. (%)	3 (21%)
Laboratory results at CMV diagnosis, median, range	
Hemoglobin (g/dL)	9.1, 7.4–11.9
Platelets ($\times 10^3$/μL)	138, 38–341
WBC ($\times 10^3$/μL)	7.7, 3–30.9
Absolute lymphocyte count ($\times 10^3$/μL)	0.5, 0–3.1
Absolute neutrophil count ($\times 10^3$/μL)	5.8, 2.6–23.4
Creatinine (mg/dL)	0.7, 0.4–5.5
ALT (IU/L)	34, 13–630
AST (IU/L)	48, 17–583
Co-infections within 1 month of hospitalization	
Significant infection[b], no. (%)	8 (57%)
C. difficile colitis	3 (21%)
Bloodstream infection	4 (29%)
Other significant infection	5 (36%)
Co-infection before CMV, no. (%)	7 (50%)
Days from coinfection to CMV, median, range	14, 3–38
Co-infection at or after CMV, no. (%)	7 (50%)
Days from CMV to coinfection, median, range	13, 0–71
Outcomes	
In-hospital mortality, no. (%)	4 (29%)
Days from CMV to death, median, range	20, 10–46
CMV recurrence, no. (%)	3 (21%)

CMV cytomegalovirus, *SLE* systemic lupus erythematosus, *HIV* human immunodeficiency virus, *IV* intravenous, *ICU* intensive care unit, *WBC* white blood count, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase

[a]Refer to descriptions of assays in "Methods"

[b]Total number of cases with significant infection. Several cases had more than one co-infection during the time period considered

CMV diagnosis, management and outcome

Twelve patients had CMV DNAemia and two had end-organ disease without viral load testing performed, including one case of CMV colitis, diagnosed by histopathology, and one of CMV pneumonitis, with a positive bronchoalveolar lavage culture. Five cases had both DNAemia and a positive test for CMV at a non-blood site (2 pulmonary and 3 gastrointestinal tract). Individual peak viral loads are shown in Table 1. Thirteen patients (93%) received antiviral therapy, the remaining patient died before treatment could be initiated. Of those treated, 11 received IV ganciclovir and 9/11 (82%) were later transitioned to oral valganciclovir; two received oral valganciclovir alone. Median antiviral duration was 33 days (range 13–171). Three (21%) received adjunctive CMV immune globulin. Three (21%) patients developed recurrent CMV disease, two were symptomatic at time of relapse, and all three were retreated. Median time to relapse was 56 days (range 15–536).

A total of 14 different co-infections were diagnosed in 8 patients (Table 1). Organisms isolated in blood cultures of four patients included methicillin-resistant *Staphylococcus aureus*, *Enterobacter cloacae*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, and *Klebsiella pneumoniae*. In two patients, two different organisms grew at different time points, 9 and 13 days apart. Pulmonary tuberculosis preceded the diagnosis of CMV in two patients. Other infections included non-typhoidal *Salmonella* gastroenteritis, abdominal candidiasis, *S. aureus* empyema and three cases of *C. difficile* infection. Half of the co-infections preceded the diagnosis of CMV by a median of 14 days.

Four patients (29%) died during their initial hospitalization (including one death prior to initiation of antiviral therapy) and an additional 2 patients also died although not until several years after their CMV episode (Table 1). Median time from CMV diagnosis to in-hospital mortality was 20 days (range 10–46).

Case–control analysis

Six cases with SLE and CMV were matched to 18 control patients. A comparison of cases and controls is shown in Table 3. For specific details regarding matching refer to the Supplementary Table. Both groups were similar with respect to age at SLE diagnosis, use of steroid-sparing immunosuppression, symptoms, and laboratory values at admission. In both groups, fever was the most common presenting symptom, affecting half of all patients. Gastrointestinal and respiratory symptoms were also common. Rash, joint pain, and fatigue at time of admission were almost exclusively seen in controls, but the differences were not statistically significant. Although fatigue was common in cases at time of CMV diagnosis, it was infrequent at the time of initial presentation. Laboratory values at admission were also similar, with no significant differences in anti-dsDNA, C3, C4, and lymphocyte counts.

Compared to controls, cases received significantly higher doses of glucocorticoids in the period leading up to admission, developed more co-infections, had a longer length of stay, and were more likely to be admitted to the ICU. The median average daily dose in prednisone equivalents was more than ten-fold higher for cases compared to controls, within 8 and 4 weeks prior to admission ($p < 0.01$). In the one-month period surrounding admission, cases developed significantly more co-infections (67% vs. 17%, $p = 0.04$).

Discussion

While CMV reactivation is known to be a major cause of morbidity and mortality in transplant recipients and patients with HIV-AIDS, its role as a pathogen in patients with underlying rheumatic disease is not well understood. In this study, we have described in detail a cohort of patients with various underlying rheumatologic comorbidities, who experienced significant clinical disease attributable to CMV, typically requiring extended hospitalization and often ICU admission. Most patients had high-level viremia, many had confirmed or suspected end-organ disease, and four patients died shortly after their diagnosis of CMV. Similar to previous studies, some patients had longstanding rheumatic disease, while others were newly diagnosed [6, 7, 16]. With increasing use of immunomodulating drugs in addition to frequent use of long-term and high-dose glucocorticoids, this is a large patient population that could be at risk from both direct and indirect clinical sequelae related to CMV reactivation.

Given the diversity of rheumatic conditions encountered and relatively high proportion of SLE patients experiencing reactivation in both our study and the published literature, we chose to focus on this subset of patients in our case control analysis. Previous studies noted difficulty in distinguishing CMV reactivation from a flare of SLE [14, 16, 25], and this was also seen in our patients. Cases and controls presented with similar constellations of symptoms, including fever, gastrointestinal, and respiratory symptoms, and the results of laboratory investigations were similar. There was a trend towards lower anti-dsDNA and higher C3 in the cases compared to controls, but these differences were not statistically significant. Overall, the clinical picture at admission was essentially indistinguishable between the two groups. Several cases were admitted with a presumed diagnosis of an SLE flare, and CMV was only considered after failure to respond to increased immunosuppression. In all of these patients, antiviral therapy was commenced only after viral load testing was positive. The major risk factor identified in

Table 3 Comparison of clinical characteristics, immunosuppression, co-infection and outcome data for cases of systemic lupus erythematosus (SLE) with CMV reactivation compared to SLE controls without CMV reactivation

Characteristics	Cases ($n=6$)	Controls ($n=18$)	P value
Demographics			
Female sex, no. (%)	6 (100%)	18 (100%)	1
Age at admission, mean ± SD	38 ± 15	36 ± 15	0.88
White race (vs. non-white)	2 (33%)	5 (28%)	0.42
Duration of rheumatologic disease at admission (years), mean ± SD	7.7 ± 7.5	9.6 ± 8	0.74
Total admissions within previous year, median, range	3, 2–4	2, 1–6	0.14
HIV negative, no. (%)	3 (50%)	9 (50%)	1
CMV seropositive, no. (%)	5 (83%)	2 (11%)	0.003
Rheumatic disease history			
Age at time of rheumatologic diagnosis, mean ± SD	30 ± 11	27 ± 16	0.62
Lupus nephritis, no. (%)	4 (67%)	10 (56%)	1
Number of admissions for disease within year, median, range	2, 0–3	1, 1–3	0.48
Glucocorticoid use			
Pulse steroids within 8 weeks of admission, no. (%)	2 (33%)	0	0.05
Average daily dose (mg) within 8 weeks admission, median, range	36.5, 6–99	2.5, 0–32	0.006
Average daily dose (mg) within 4 weeks admission, median, range	30, 6–58	2.5, 0–34	0.007
Started on steroids during admission, no. (%)	0	7 (39%)	0.13
Pulse-dose steroids during admission, no. (%)	3 (50%)	10 (71%)	1
Average daily dose (mg) during admission, median, range	60, 27–325	224, 5–650	0.50
Steroid-sparing immunosuppression			
Within 3 months admission			
Biologic agent, no. (%)	1 (17%)	1 (6%)	0.45
Other immunosuppression, no. (%)	4 (67%)	10 (56%)	1
Started on steroid-sparing agent during admission, no. (%)	2 (33%)	8 (44%)	1
Admission details			
Year of admission, median, range	2008, 2004–2011	2009, 2006–2012	0.33
Length of stay, median, range	47, 8–86	7, 1–32	0.006
Admitted to ICU, no. (%)	4 (67%)	2 (11%)	0.02
Dialysis at admission, no. (%)	0	1 (6%)	1
Symptoms at time of admission, no. (%)			
Fever/chills	3 (50%)	8 (44%)	1
Fatigue	0	3 (17%)	0.55
Weight loss	1 (17%)	4 (22%)	1
Joint pain	1 (17%)	8 (44%)	0.35
Rash	0	4 (22%)	0.54
GI symptoms	3 (50%)	7 (39%)	0.67
Respiratory symptoms	2 (33%)	6 (33%)	1
Other symptoms	3 (50%)	5 (28%)	0.36
Laboratory results			
Anti-dsDNA, units/mL, median, range	39, 14.6–201	122, 6–201 ($n=15$)	0.26
C3, mg/dL, median, range	72, 42–116	46, 24–111	0.08
C4, mg/dL, median, range	9.2, 5.3–26.4	12, 4–41	0.40
At admission, median, range			
Hemoglobin (g/dL)	8.9, 5.1–13.5	10.5, 8.8–13.2	0.14
Platelets ($\times 10^3$/μL)	234, 120–301	241.5, 21–310	0.87
White blood cell count ($\times 10^3$/μL)	7.1, 1.4–13.5	6.2, 0.6–14.3	0.59
Absolute lymphocyte count ($\times 10^3$/μL)	0.7, 0.4–2.7	0.85, 0.1–2.9	0.95
Absolute neutrophil count ($\times 10^3$/μL)	4.3, 0.5–11.3	4.6, 0.4–12.9	0.69
Creatinine (mg/dL)	0.9, 0.58–1.88	0.82, 0.52–10.14	0.97

Table 3 (continued)

Characteristics	Cases ($n=6$)	Controls ($n=18$)	P value
At discharge, median, range			
Hemoglobin ($\times 10^3$/μL)	8.7, 7.6–11.3	10.1, 7.4–12.8	0.37
Platelets ($\times 10^3$/μL)	264, 122–505	242, 84–327	0.57
White blood cell count ($\times 10^3$/μL)	8.1, 3.1–15	6.9, 1.4–14.6	0.50
Absolute lymphocyte count ($\times 10^3$/μL)	0.55, 0.2–3.5	1.0, 0.1–3.5	0.14
Absolute neutrophil count ($\times 10^3$/μL_	5.4, 2.7–12.6	5.0, 0.5–12.2	0.58
Creatinine (mg/dL)	0.55, 0.13–2.2	0.74, 0.37–9.54	0.23
Co-infections			
Any co-infection, no. (%)	4 (67%)	3 (17%)	0.04
C. difficile colitis	2 (33%)	0	0.05
Bloodstream infection	3 (50%)	3 (17%)	0.14
Other	2 (33%)	1 (6%)	0.14
Outcome			
Death in hospital or within 90 days, no. (%)	1 (17%)	0	0.25

CMV cytomegalovirus, *SD* standard deviation, *HIV* human immunodeficiency virus, *ICU* intensive care unit, *dsDNA* double-stranded DNA, *C3/4* complement 3/4

the SLE subgroup was the use of high-dose glucocorticoids, which is biologically plausible given our understanding of the immunobiology of CMV reactivation [26] and consistent with previous studies [10, 13].

Co-infections were common, affecting half of our cohort, and those with co-infections tended to have more than one. Of the eight patients with clinically significant co-infection, seven required ICU admission at some point during their index admission. Prior studies have found similar rates of co-infections [6, 7], but the organisms seen vary. In our study, there were many bacterial infections, few fungal infections, and no non-CMV viral infections. Interestingly, two patients developed (presumed) reactivation of latent tuberculosis just prior to their episode of CMV, which could be reflective of impaired T-cell immunity. It is unclear if these co-infections somehow increased the likelihood of CMV reactivation, were related to the secondary immunosuppressive effects of CMV itself, are reflective of underlying comorbidities and extended hospitalization, or simply serve as a marker for the overall level of immunosuppression.

There are some limitations that should be considered when interpreting our results. This was a small, retrospective study with statistical power limited by the sample size and number of outcomes. Despite extending our search over a 15-year study period, we were only able to identify six patients with SLE and proven CMV reactivation for comparison, and the other non-SLE patients were too diverse to directly compare. Whether the low numbers were due to the rarity of this combination of events, or from under-diagnosis due to lack of testing in this population is unclear. Rates of CMV antibody testing in both cases and controls were low, so we could not be certain that all cases were truly reactivation rather than primary disease, nor that all controls were at risk of reactivation. However, given the known high seroprevalence of CMV, particularly amongst older adults, we assumed that most patients were likely to be CMV seropositive [2]. It is also possible that some control patients could have had CMV reactivation given that viral load testing was not performed in these individuals. Finally, quantification of glucocorticoid use was difficult; steroid regimens can be complex and often change as patients respond (or fail to respond) to therapy. However, after examining glucocorticoid use in multiple ways it was clear that SLE cases had received significantly greater amounts prior to admission compared to controls.

In conclusion, we have demonstrated that symptomatic CMV reactivation occurs in patients with rheumatic disease, and is associated with significant morbidity and mortality. Clinicians should consider appropriate diagnostic testing for CMV during the evaluation of fevers in this patient population, especially in those with an apparent flare of their underlying disease that does not respond to immunosuppressive therapy. High doses of glucocorticoids appear to be a risk factor for CMV reactivation, as well as prolonged hospitalization and other infections. Routine antibody testing, and potentially CMV-specific immune biomarker testing, could be considered prior to the initiation of high dose steroids to identify those at-risk for CMV reactivation. Additional studies are needed to better define the role of virologic surveillance, therapeutic and prophylactic antivirals, and to improve the understanding of the risk factors and pathogenesis of CMV reactivation in this complex patient population.

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Author contributions BG was involved in all aspects of this project including study design, data collection, analysis, interpretation and manuscript preparation. EH and RB contributed to data collection and manuscript preparation. JC and DS provided oversight and assisted with study design, analysis and manuscript editing. All authors read, contributed to and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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Compliance with ethical standards

Conflict of interest DRS reports being on advisory boards for Merck, Shire, Chimerix, Takeda and Moderna and being a grant recipient from Merck, Summit, Actelion, Tetraphase and Seres Therapeutics. All other authors report no potential conflicts of interest.

Ethical standards This study was approved by the Tufts Medical Center institutional review board (July 12, 2017, Approval Number 12618) and performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent Informed consent was not required given its retrospective nature and minimal risk.

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