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ORIGINAL ARTICLE

Cytomegalovirus infection is associated with venous thromboembolism of immunocompetent adults—a case–control study

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Abstract Cytomegalovirus (CMV) seems to contribute to the development of venous thromboembolism (VTE) in immunocompromised patients whereas literature data on the role in immunocompetent individuals are mainly limited to case reports. This study aimed to investigate if cytomegalovirus infection contributes to the development of VTE in immunocompetent individuals. CMV-IgG and CMV-IgM antibody titres, CMV-IgG avidity and CMV-DNA were identified in samples from 166 VTE patients and from 166 healthy blood donors matched for gender and age. CMV-IgG antibodies were found more frequently in VTE patients compared to controls [57.8% vs. 44.0%; adjusted OR 1.75 (95% CI 1.13–2.70); p=0.016]. Accordingly, median CMV-IgG titres were significantly higher in the case group (89.4 vs. 1.8 AU/ml; p=0.002). Although the overall rate was low, CMV-IgM antibodies were detected more often among cases than controls. The difference was significant in patients with an unprovoked VTE event [7.4% vs. 0.6%; adjusted OR 5.26 (95% CI 1.35–20.8); p= 0.017]. CMV-IgG antibodies of almost all VTE patients (98.9%) and controls (98.6%) were found to be of high avidity. The rate of positive CMV-DNA samples was low and not different between cases and controls. With the exception of age, no association was found between CMV seropositivity and established VTE risk factors within the VTE group. CMV infection seems to play a role in the development of VTE in immunocompetent patients. Recurrent infection might be more important than acute CMV infection.

Keywords CMV · Infection · Venous thromboembolism · IgG · IgM · Antibodies

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Introduction

Acute infections are associated with a transient increased risk of venous thromboembolism (VTE) [1]. The direct infection of endothelial cells as well as a systemic inflammatory response may lead to haemostatic abnormalities that range from insignificant laboratory changes to severe disseminated intravascular coagulation [2].

Endothelial cells can be directly infected by different viruses. A procoagulant activity has been reported for cytomegalovirus (CMV), herpes simplex virus type 1 and type 2, varicella zoster virus, and HIV infection [2–6]. In particular, CMV has been suggested to play a role in the pathophysiology of venous thromboembolic events [3, 7, 8]. The majority of reports focus on immunocompromised

patients with HIV-associated disease or immunosuppression related to transplantation [9–12]. More recently, a number of case reports have been published that suggest CMV may also be involved in the development of VTE in immunocompetent individuals [13–20]. Even though some case studies suggest a causative role for CMV, no systematic study has thus far been published investigating the role of CMV in this group. We initiated this investigation to address the potential role of CMV in immunocompetent individuals in a case–control study design using adequate laboratory testing to allow for reliable diagnostic evaluation of CMV infection.

Subjects and methods

Study population

Patient data were obtained from the MAin-ISar-THROmbosis (MAISTHRO) Registry, beginning in March 2000 and continuing through February 2010. One thousand five hundred patients who were referred to our university hospital's outpatient department were enrolled with acute or a documented history of VTE [i.e. lower extremity deep vein thrombosis (DVT) and/or pulmonary embolism (PE)]. The registry was approved by the local ethics committee, and all patients provided written informed consent. The design of the MAISTHRO Registry has been described previously [21, 22]. In brief, detailed clinical data with regard to VTE, information about the presence or absence of VTE risk factors and the results of technical and laboratory investigations, including screening for thrombophilic disorders, were entered into the database. Patients were considered to have a family history for VTE if at least two first degree relatives were previously affected by a venous thromboembolic event.

For the current analysis, 166 consecutive patients aged 18 to 70 years after a first VTE episode treated at the Johann Wolfgang Goethe University Hospital Frankfurt/Main (Germany) were included. Additional inclusion criteria comprised: (1) absence of clinically relevant immunosuppression (transplantation, medical immunosuppression and HIV infection) and (2) absence of malignant disease which was either present at the time of VTE manifestation or diagnosed during the acute VTE course. Patients' characteristics are presented in Table 1. Patients were compared to 166 healthy blood donors without a history of VTE that served as controls and were matched for age (±5 years) and gender (1:1 approach).

Table 1 Patients' characteristics and prevalence of common VTE risk factors (N=166)

	N	%
Male gender	70	42.2
Spontaneous VTE	55	33.1
Proximal DVT	58	34.9
Distal DVT	98	59.0
Symptomatic pulmonary embolism	45	27.1
Long-term travel	19	11.4
Previous surgery	32	19.3
Immobilization	46	27.7
Inflammation	12	7.2
Hormonal treatment	48	50.0[a]
Pregnancy and puerperium	7	7.3[a]
Hereditary thrombophilia	45	32.8
Elevated FVIII activity	45	29.2
Antiphosphopid antibodies	3	1.9
History of VTE	13	7.8

VTE venous thromboembolism, *DVT* deep vein thrombosis, *FVIII* factor VIII

[a] Percentages related to females only

Diagnosis of venous thromboembolism

Diagnosis of DVT was made by venous compression ultrasound examination and/or by contrast-mediated venography. Diagnostic procedures for PE in the acute setting were only performed if patients presented with typical clinical symptoms. For the diagnosis of symptomatic PE, patients underwent a multidetector spiral CT scan or ventilation–perfusion lung scanning.

Unprovoked and risk-associated venous thromboembolism

Risk-associated VTE was considered if the VTE was related to the following risk factors: long-term travel (> 6 h), surgical intervention within the last 4 weeks, immobilization for longer than 3 days, inflammation, hormonal treatment or pregnancy. Inflammation was defined as either an acute infection or a chronic inflammatory disease (e.g. inflammatory bowel disease, rheumatoid arthritis or systemic lupus erythematosus). Patients with immunosuppression due to an infection itself (e.g. HIV) or due to medical treatment were excluded from the study. If thrombosis was not related to one of the aforementioned risk factors, the condition was considered an unprovoked DVT. According to these criteria, patients with hereditary thrombophilic disorders were also classified as having an unprovoked VTE.

Serological parameters of CMV infection

Blood sampling was performed within 90 days after the diagnosis of VTE ("acute phase") or after a time interval of at least 180 days ("post-acute phase"). The rationale for the choice of these time intervals for blood sampling was based

on the assumption that if primary CMV infection contributed to the development of VTE, one would be expected to find markers of acute CMV infection (i.e. CMV-IgM and CMV-DNA) more frequently in the "acute phase" group. In contrast, CMV-IgG antibodies of high avidity maturate over time and are expected to be more frequently detected in subjects with non-primary CMV infection as well as in the "post-acute phase" group.

Different serological parameters of a CMV infection including CMV-IgG, CMV-IgM and CMV-IgG avidity were measured in citrated plasma samples using colorimetric assays on an automated immunological analyser (Architect®, Abbott Diagnostics, Abbott Park, IL, USA). For CMV-IgG, CMV-IgM and CMV-IgG avidity testing, plasma samples were analysed according to standard manufacturer's instructions. The established assay cut-off values provided by the manufacturer were used to designate a sample as CMV-IgG or CMV-IgM positive. Due to the unknown relevance, individuals with an intermediate result on CMV-IgM testing (grey zone result; 3 of 332 study participants) were excluded from the statistical analysis with respect to this parameter.

For CMV-IgG avidity testing, the plasma sample was preincubated with a CMV lysate and subjected to the standard CMV-IgG assay. For the determination of the avidity index, absorbance values from IgG testing without lysate preincubation were compared to values with preincubation. Avidity was considered to be "high" if the ratio was found to be >60%. A sample was assigned "intermediate" if the ratio was 50% to 60%. An avidity index <50% was considered to be "low". CMV-IgG antibodies with a high avidity based on this assay favoured a time point of infection greater than 6 months [23, 24].

Determination of CMV-DNA

Only matched case–control pairs with a sufficient sample volume after serological testing were considered for this analysis. For CMV-DNA detection, 200 μl of citrated plasma were extracted using a standard column DNA blood mini kit extraction (Qiagen, Hilden, Germany). Eluted nucleic acid probes were subjected to an in-house real-time PCR CMV-DNA assay on a StepOne platform (Applied Biosystems, Foster City, CA, USA) and assayed in two independent PCR experiments.

Laboratory testing for VTE risk factors

Screening for thrombophilia included testing for the factor V Leiden mutation (FVL), the prothrombin G20210A mutation (PT), antiphospholipid antibodies, and antithrombin (AT), protein C (PC), protein S (PS) and factor VIII activities, as previously described [22].

Data comparison and statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS version 17.0; SPSS, Chicago, IL, USA). In addition to descriptive statistics, we performed a Chi-square test in cross-tabulations and the Mann–Whitney *U* test for comparison of metric variables. The criterion for statistical significance was a p value less than 0.05. Patients were compared to control subjects in matters of CMV serostatus and the relative risks were estimated by calculating odds ratios (OR) and corresponding 95% confidence intervals (95% CI). Odds ratios were adjusted for gender and age with logistic regression methods. Due to small patient numbers with regard to CMV seropositivity, calculations were performed using a Fisher's exact test and Monte Carlo's method. Binary logistic regression analysis using a stepwise backward regression after WALD was performed to analyse for an association between CMV seropositivity and the presence of established VTE risk factors in the patient group. Results are also presented in box plots with the bare length indicating the interquartile range (25th–75th percentile). Outliers were defined as values differing by 1.5–3.0 bare lengths, and extreme values were those differing >3.0 box lengths from the upper or lower edge of the box. In the figures, outliers are illustrated as circles and extreme values as stars.

Results

Baseline characteristics of the study population

The 166 patients with VTE included 96 females (57.8%) and 70 males (43.2%). The mean age was 43.2±13.5 years at onset of the first episode of VTE among cases and 43.0± 13.6 years among controls (p=0.881). The VTE group was comprised of 121 (72.9%) patients with an isolated lower extremity DVT, 10 patients (6.0%) with an isolated PE and 35 patients (21.1%) with a DVT complicated by a PE. VTE was associated with risk factors (i.e. long-term travel, previous surgery, immobilization, inflammation, hormonal treatment or pregnancy) in 111 cases (66.9%) and occurred unprovokedly in 55 cases (33.1%). Laboratory testing was performed within 90 days ("acute"; n=74) or after at least 180 days ("post-acute"; n=92) after the diagnosis of VTE. None of our patients presented with clinical symptoms of acute CMV infection.

CMV serostatus in VTE patients compared to controls

CMV-IgG-positive patients were found more frequently in the VTE group compared to the control group [57.8% vs.

44%, respectively; adjusted OR 1.75 (95% CI 1.13–2.70); p=0.016]. The odds ratio was even higher in the subgroup of patients with an unprovoked thromboembolic event [63.6% vs. 44.0%; adjusted OR 2.17 (1.15–4.14); p= 0.017]. The results of the laboratory testing are summarized in Table 2. Additionally, in the subgroup of CMV-IgG-positive individuals, the median CMV-IgG titre was significantly higher in patients who developed VTE when compared to controls, 89.4 (25–75% percentile 0.8–220.9) vs. 1.75 AU/ml (0.7–135.3); p=0.002; see Fig. 1.

Although the overall number of CMV-IgM-positive samples was low, a higher frequency of positive results were observed in the VTE group as compared to controls [4.3% vs. 0.6%; OR 7.3 (95% CI 0.9–60.1); p=0.037]. In the subgroup of VTE patients with an unprovoked thromboembolic event, the difference was also found to be significant [7.4% vs. 0.6%; adjusted OR 5.26 (1.35–20.8); p=0.017].

With the exception of two samples, all CMV-IgG-positive patients that were subjected to avidity testing were found to have CMV antibodies with a high avidity (161 of 163; 98.8%). One individual with intermediate avidity was found in each of the VTE and the control groups. The VTE patient with intermediate avidity was IgM positive while the control individual was IgM negative.

CMV serostatus in VTE subgroups of "acute" and "post-acute" sample acquisition

Cases were divided into two subgroups according to the time interval between the VTE diagnosis and acquisition of blood for laboratory testing [≤90 days ("acute phase", n=74) or ≥180 days ("post-acute phase", n=92)]. No significant difference was found with regard to serological or molecular–biological markers of CMV infection between these two patient groups. CMV-IgG and IgM antibodies were detected in 56.8% vs. 59.8% and 2.8% vs. 5.4% of patients in the "acute" and "post-acute" phase, respectively (p = ns). In particular, there was no difference in the rate of CMV-IgM or CMV-DNA-positive samples. Only two out of seven CMV-IgM-positive patients were detected in the "acute phase", in these cases, CMV-IgG antibodies were of high avidity.

CMV-DNA in VTE patients compared to controls

Overall CMV-DNA was detected in a low number of samples (4 of 104; 3.9%; see Table 2). If DNA was detected, the titres were below 10^3 DNA copies/ml. In the VTE group, as well as in the control group, two CMV-DNA-positive samples were found. Interestingly, there was no correlation between CMV-IgM as a potential marker for CMV replication and CMV-DNA results. On the contrary, all CMV-IgM-positive individuals in both groups were found to be negative by DNA testing.

Analysis of VTE risk factors

Because the frequency of VTE risk factors was only known in the group of VTE patients, this analysis was limited to the case group. Table 3 shows the distribution of thrombophilia and other established VTE risk factors according to CMV-IgG positivity. By means of binary logistic regression analysis including age, gender and the presence or absence

Table 2 CMV serologic testing in VTE patients and controls subjects

Total cohort		VTE patients (n=166)	Controls (n=166)	OR (95% CI)	p value
CMV-IgG	Positive (n)	96/166	73/166	1.75 (1.13–2.70)	0.016
	Positive (%)	57.8	44.0		
	AU/ml (mean)	182.7	82.1	NA	0.002
	AU/ml (median)	89.4	1.8		
	IQR	0.8–220.9	0.7–135.3		
CMV-IgM	Positive (n)[a]	7/164	1/165	7.30 (0.89–58.9)	0.037
	Positive (%)	4.3	0.6		
	Index (mean)	0.32	0.23	NA	0.066
	Index (median)	0.21	0.18		
	IQR	0.14–0.32	0.14–0.26		
CMV-IgG "high avidity"	Positive (n)	92/93	69/70	NA	NA
	Positive (%)	98.9	98.6		
CMV-DNA (PCR)	Positive (n)	2/52	2/52	NA	NA
	Positive (%)	3.9	3.9		

IQR interquartile range, *NA* not applicable, *VTE* venous thromboembolism

[a] One case/two controls with result "grey zone" were excluded from the analysis

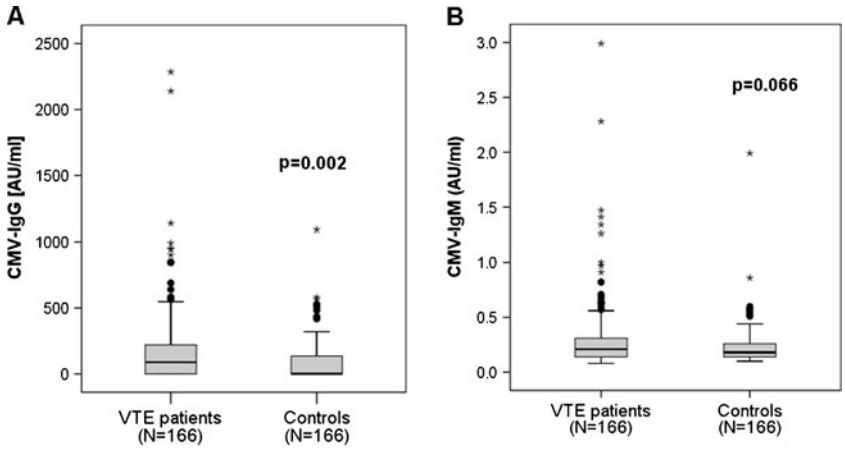

Fig. 1 Quantitative CMV-IgG and CMV-IgM titres in VTE patients and healthy controls. CMV-IgG (**a**) and CMV-IgM titres (**b**) were higher in patients who developed VTE when compared to controls. However, the difference of CMV-IgM titres did not reach statistical significance

of thrombopilia and other VTE risk factors, a significant association with CMV-IgG serostatus could only be demonstrated for age. Patients with a positive result for CMV-IgG were found to be older than CMV-IgG-negative individuals [median age 46.0 vs. 39.6; OR 1.05 (1.01–1.07); p=0.020]. In contrast, CMV-IgG-positive patients were less likely to have hereditary thrombophilia (i.e. FVL mutation, PT mutation or deficiencies of AT, PC or PS) [25.3% vs. 41.9%; OR 0.47 (0.23–0.97); p=0.046].

The clinical characteristics of CMV-IgM-positive patients are presented in Table 4. Three out of seven VTE events were related to pregnancy or the use of hormonal contraceptives in women. No additional risk factors were found in these patients. At least one thrombophilic disorder was detected in six of seven patients. However, the number of cases is too small to draw any definitive conclusions.

Table 3 Thrombophilia and VTE risk factor distribution according to CMV-IgG seropositivity

	CMV-IgG negative		CMV-IgG positive		p value
	n	%	n	%	
Male gender	29	41.4	41	42.7	0.875
Long-term travel	8	11.4	11	11.5	1.000
Previous surgery	10	14.3	22	22.9	0.232
Immobilization	20	28.6	26	27.1	0.862
Inflammation	5	7.1	7	7.3	1.000
Hormonal treatment	25	35.7[a]	23	24.0[a]	0.063
Pregnancy and puerperium	3	4.3[a]	4	4.2[a]	1.000
Hereditary thrombophilia	26	41.9	19	25.3	0.046
Elevated FVIII activity	16	23.9	29	33.3	0.216
Antiphospholipid antibodies	1	1.5	2	2.2	1.000
Family history of VTE	6	8.6	7	7.3	0.777

FVIII factor VIII, *VTE* venous thromboembolism

[a] Percentages related to females only

Discussion

Cytomegalovirus infection is usually characterized by a self-limited, acute infection and asymptomatic chronic carrier status with intermittent virus reactivation [25–27]. The rate of seropositive individuals increases with age. In adults, prevalence ranges from 30% to more than 90%, depending on various factors, including, for example, the socioeconomic status [28, 29]. In the last few years, a number of studies have been published that demonstrated an association of CMV infection with the development of VTE. The research groups focused primarily on the role of CMV infection in immunocompromised patients [9–12, 30]. More recently, an increasing number of observations also support a role for CMV infection in immunocompetent individuals [14, 15, 18, 20, 31]. However, these findings are mainly based on case reports or case series [3]. In addition, an appropriate control group has mostly been lacking and the diagnostic evaluation of markers of CMV infection has frequently been incomplete. Some authors have verified the clinical diagnosis of CMV infection by means of single CMV-IgM testing, but low positive titres of IgM antibodies can lead to false-positives and might be induced by other immunostimulatory events like EBV-associated infectious mononucleosis or other viral and non-viral infections [32, 33]. In a recently published case–control study including 140 patients with acute CMV infection and 140 consecutive matched subjects in whom acute CMV infection was excluded, 4 patients (2.9%) suffered from venous thrombosis compared to none in the control group (p=0.045) [31]. Overall, there is only weak evidence that CMV infection might play an important role in the development of VTE in immunocompetent patients.

This investigation therefore aimed to investigate systematically the role of CMV infection in the development of VTE in immunocompetent patients. The retrospective case–control design ensures control of the important variables, age and sex, that might influence the study results. The

Table 4 Clinical characteristics of CMV-IgM-positive VTE patients (N=7)

Age	Sex	VTE	VTE risk factors	Thrombophilia
29	F	Distal DVT + PE	Pregnancy	APL
31	F	Distal DVT	Oral contraceptive	FVIII
37	F	Proximal DVT	Oral contraceptive	–
58	M	Proximal DVT	–	FVIII
61	F	Proximal DVT	–	FVL
42	F	Proximal DVT	–	FVIII, FVL
46	F	Proximal DVT	–	–

F female, *M* male, *DVT* deep vein thrombosis, *PE* pulmonary embolism, *APL* antiphospholipid antibodies, *FVIII* elevated factor VIII, *FVL* factor V Leiden mutation

comparison to an appropriate control group of markers of CMV infection in the VTE group is especially important because subclinical or asymptomatic CMV reactivations are known to be quite frequent in immunocompetent individuals [25–27]. The comprehensive laboratory testing might allow for a more complete insight into the role of CMV infection in the development of VTE.

Our data favour the importance of recurrent, and not acute, CMV infection in its relationship with VTE development. The results are suggestive of a significant time interval between primary CMV infection and clinically overt VTE disease. Thus, the rate of individuals with prior CMV infection, represented by the number of CMV-IgG-positive samples, is significantly higher in the group of VTE patients compared to healthy controls. Because CMV-IgG basically reflects a prior CMV infection, it can be concluded from these results that individuals with VTE disease are more likely to be CMV carriers.

Moreover, CMV-IgG antibodies almost exclusively had a high avidity. CMV-IgG avidity testing has been shown to be useful for distinguishing primary and non-primary infections [23, 24]. It measures the binding affinity of IgG antibodies. At the onset of infection, IgG antibodies of low avidity is produced. Over time, maturation of the antibodies occurs, resulting in an increased binding affinity and, thus, a higher avidity. Primary CMV infection, therefore, can be dated back at least 6 months prior to the laboratory testing. Considering the low number of CMV-IgM-positive samples, it seems to be even more likely that the primary CMV infection had occurred several months or years prior to clinically overt VTE disease. Additionally, the comparative analysis of cases with a time interval between VTE manifestation and acquisition of blood for laboratory testing of ≤90 days compared to ≥180 days supports this hypothesis. In line with the hypothesis that late primary or recurrent, but not acute primary, CMV infection is related to VTE development, there was no significant difference with respect to markers of acute or primary CMV infection between these two groups.

The quantitative serological and molecular biological testing supports this view. Thus, the median CMV-IgG titres are significantly higher in the case group when compared to controls (89.4 vs. 1.8 AU/ml). Even though this partially reflects the larger number of CMV-IgG-positive individuals in the case group, it also points towards a higher rate of recurrent infections because IgG titres are known to increase secondary to repetitive immunological reactions to the pathogen. While the overall number of CMV-DNA-positive samples was very low, there was also no difference with regard to DNA positivity between the case and the control groups. Considering the fact that active CMV replication can typically be found up to months or even years after the primary infection, the results clearly demonstrate that a recent primary infection is highly unlikely in this cohort.

Taken together, our study results are in clear contrast to the sparse published data. Available literature results favour primary CMV infection as a causative event in the development of VTE in immunocompetent individuals [14, 15, 18, 20].

The link between CMV infection and VTE development remains elusive. CMV may exert its procoagulant properties by expression of tissue factor and procoagulant phospholipids on the EC surface that may lead to enhanced adherance of monocytes and leucocytes to the endothelium [3, 18, 33]. In consequence, an increased production of interleukin-6, derived from infected endothelial cells and monocytes, and an increased expression of cell surface receptor CD40 and von Willebrand factor may contribute to thrombogenesis. Furthermore, it seems possible that CMV infection can induce antiphospholipid antibodies [34, 35]. According to a previous study, CMV-IgG serostatus was linked to an unexplained factor VIII elevation [36]. This finding is in line with other studies that described an assocation of cytomegalovirus infection with an elevation of procoagulant factors such as factor VIII and fibrinogen [30, 37]. Even though our study was not designed to explain the etiological link between CMV infection and VTE development, our results point towards a prolonged time interval between the two events.

This study is limited by its retrospective design. Even though important variables like age and gender are

controlled by the case–control study design, the presence of other confounding factors cannot be excluded. However, apart from hereditary thrombophilia which was more frequently detected among CMV-IgG-negative patients, there was no significant difference in the distribution of other established VTE risk factors according to CMV-IgG serostatus. Moreover, because of a mean age of 43 years for the cohort of VTE patients, severe and potentially confounding comorbidities are less likely than in elderly patient cohorts. In addition, it has to be taken into account that due to limitations in sample volume, CMV-IgG avidity and CMV-DNA could not be analysed in the complete cohort. Finally, healthy blood donors served as controls. This might be a source of selection bias because they are checked regularly on behaviour related to general health and infections. So the prevalence of CMV infection will most likely be lower in this control group than in the general population, which will lead to an overestimation of the results. However, a previous CMV infection is not a criterion for exclusion from blood donation. On the other hand, to date, there are no comparative studies investigating the association between CMV serostatus and the occurrence of venous thromboembolism.

In conclusion, CMV infection may play a role in the development of VTE in immunocompetent patients. Our data suggest that recurrent, i.e. either reactivation or re-infection, and not primary CMV infection precedes disease onset and ultimately results in VTE development. The definitive role of CMV in VTE development and the involved pathological processes have to be clarified by future investigations.

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References

1. Smeeth L, Cook C, Thomas S, Hall AJ, Hubbard R, Vallance P (2006) Risk of deep vein thrombosis and pulmonary embolism after acute infection in a community setting. Lancet 367 (9516):1075–1079
2. Keller TT, Mairuhu AT, de Kruif MD, Klein SK, Gerdes VE, ten Cate H, Brandjes DP, Levi M, van Gorp EC (2003) Infections and endothelial cells. Cardiovasc Res 60(1):40–48
3. Squizzato A, Gerdes VEA, Bueller HR (2005) Effects of human cytomegalovirus infection on the coagulation system. Thromb Haemost 93(3):403–410
4. Friedman HM (1989) Infection of endothelial cells by common human viruses. Rev Infect Dis 11(Suppl 4):S700–S704
5. Sullivan PS, Dworkin MS, Jones JL, Hooper WC (2000) Epidemiology of thrombosis in HIV-infected individuals. The Adult/Adolescent Spectrum of HIV Disease Project. AIDS 14 (17):321–324
6. Erbe M, Rickerts V, Bauersachs RM, Lindhoff-Last E (2003) Acquired protein C and protein S deficiency in HIV-infected patients. Clin Appl Thromb Hemost 9(4):325–331
7. Squizzato A, Ageno W, Cattaneo A, Brumana N (2007) A case report and literature review of portal vein thrombosis associated with cytomegalovirus infection in immunocompetent patients. Clin Infect Dis 44(2):e13–e16
8. Rafailidis P, Mourtzoukou EG, Varbobitis IC, Falagas ME (2008) Severe cytomegalovirus infection in apparently immunocompetent patients: a systematic review. Virol J 5:47
9. Garcia I, Fainstein V, Rios A, Luna M, Mansell P, Reuben J, Hersh E (1983) Nonbacterial thrombotic endocarditis in a male homosexual with Kaposi's sarcoma. Arch Intern Med 143(6):1243–1244
10. Bagley PH, Scott DA, Smith LS, Schillaci RF (1986) Cytomegalovirus infection, ascending myelitis, and pulmonary embolus. Ann Intern Med 104(4):587
11. Kazory A, Ducloux D, Coaquette A, Manzoni P, Chalopin JM (2004) Cytomegalovirus-associated venous thromboembolism in renal transplant recipients: a report of 7 cases. Transplantation 77 (4):597–599
12. Lijfering WM, de Vries AP, Veeger NJ, van Son WJ, Bakker SJ, van der Meer J (2008) Possible contribution of cytomegalovirus infection to the high risk of (recurrent) venous thrombosis after renal transplantation. Thromb Haemost 99(1):127–132
13. Arav-Boger R, Reif S, Bujanover Y (1995) Portal vein thrombosis caused by protein C and protein S deficiency associated with cytomegalovirus infection. J Pediatr 126(4):586–588
14. Labarca JA, Rabaggliati RM, Radrigan FJ, Rojas PP, Perez CM, Ferres MV, Acuna GG, Bertin PA (1997) Antiphospholipid syndrome associated with cytomegalovirus infection: case report and review. Clin Infect Dis 24(2):197–200
15. Ofotokun I, Carlson C, Gitlin SD, Elta G, Singleton TP, Markovitz DM (2001) Acute cytomegalovirus infection complicated by vascular thrombosis: a case report. Clin Infect Dis 32(6):983–986
16. Abgueguen P, Delbos V, Chennebault JM, Payan C, Pichard E (2003) Vascular thrombosis and acute cytomegalovirus infection in immunocompetent patients: report of 2 cases and literature review. Clin Infect Dis 36(11):E134–E139
17. Youd P, Main J, Jackson E (2003) Cytomegalovirus infection and thrombosis: a causative association? J Infect 46(2):141–142
18. Fridlender ZG, Khamaisi M, Leitersdorf E (2007) Association between cytomegalovirus infection and venous thromboembolism. Am J Med Sci 334(2):111–114
19. Ergas D, Herskovitz P, Skurnik Y, Mavor E, Sthoeger ZM (2008) Superior mesenteric vein thrombosis with pulmonary embolism: a rare presentation of acute cytomegalovirus infection. Isr Med Assoc J 10(3):235–236
20. Ladd AM, Goyal R, Rosainz L, Baiocco P, DiFabrizio L (2009) Pulmonary embolism and portal vein thrombosis in an immunocompetent adolescent with acute cytomegalovirus hepatitis. J Thromb Thrombolysis 28(4):496–499
21. Lindhoff-Last E, Bauersachs R, Jesgarz J, Bergh B, Spannagl M, Schramm W (2001) The German thrombophilia registry. Ann Hematol 80(suppl1):A43
22. Linnemann B, Schindewolf M, Zgouras D, Erbe M, Jarosch-Preusche M, Lindhoff-Last E (2008) Are patients with thrombophilia and previous venous thromboembolism at higher risk to arterial thrombosis? Thromb Res 121(6):743–750
23. Lazzarotto T, Spezzacatena P, Pradelli P, Abate DA, Varani S, Landini MP (1997) Avidity of immunoglobulin G directed against human cytomegalovirus during primary and secondary infections

in immunocompetent and immunocompromised subjects. Clin Diagn Lab Immunol 4(4):469–473
24. Lagrou K, Bodeus M, van Ranst M, Goubau P (2009) Evaluation of the new architect cytomegalovirus immunoglobulin M (IgM), IgG, and IgG avidity assays. J Clin Microbiol 47(6):1695–1699
25. Kano Y, Shiohara T (2000) Current understanding of cytomegalovirus infection in immunocompetent individuals. J Dermatol Sci 22(3):196–204
26. Taylor GH (2003) Cytomegalovirus. Am Fam Physician 67 (3):519–524
27. Gandhi MK, Khanna R (2004) Human cytomegalovirus: clinical aspects, immune regulation, and emerging treatments. Lancet Infect Dis 4(12):725–738
28. Vancíková Z, Dvorák P (2001) Cytomegalovirus infection in immunocompetent and immunocompromised individuals—a review. Curr Drug Targets Immune Endocr Metabol Disord 1 (2):179–187
29. Just-Nübling G, Korn S, Ludwig B, Stephan C, Doerr HW, Preiser W (2003) Primary cytomegalovirus infection in an outpatient setting—laboratory markers and clinical aspects. Infection 31 (5):318–323
30. Mulder R, Tichelaar YI, Sprenger HG, Mulder AB, Lijfering WM (2011) Relationship between cytomegalovirus infection and procoagulant changes in human immunodeficiency virus-infected patients. Clin Microbiol Infect 17(5):747–749
31. Atzemony L, Halutz O, Avidor B, Finn T, Zimmerman O, Steinvil A, Zeltser D, Giladi M, Justo D (2010) Incidence of cytomegalovirus-associated thrombosis and its risk factors: a case-control study. Thromb Res 126(6):e439–e443
32. Park JM, Shin JI, Lee JS, Jang YH, Kim SH, Lee KH, Lee CH (2009) False positive immunoglobulin M antibody to cytomegalovirus in child with infectious mononucleosis caused by Epstein-Barr virus infection. Yonsei Med J 50 (5):713–716
33. Takatsuka H, Wakae T, Mori A, Okada M, Fujimori Y, Takemoto Y, Okamoto T, Kanamaru A, Kakishita E (2003) Endothelial damage caused by cytomegalovirus and human herpesvirus-6. Bone Marrow Transplant 31(6):475–479
34. Gharavi AE, Pierangeli SS, Harris EN (2003) Viral origin of antiphospholipid antibodies: endothelial cell activation and thrombus enhancement by CMV peptide-induced APL antibodies. Immunobiology 207(1):37–42
35. Delbos V, Abgueguen P, Chennebault JM, Fanello S, Pichard E (2007) Acute cytomegalovirus infection and venous thrombosis: role of antiphospholipid antibodies. J Infect 54 (1):e47–e50
36. Schambeck CM, Hinney K, Gleixner J, Keller F (2000) Venous thromboembolism and associated high plasma factor VIII levels: linked to cytomegalovirus infection? Thromb Haemost 83(3):510–501
37. Nieto FJ, Sorlie P, Comstock GW, Wu K, Adam E, Melnick JL, Szklo M (1997) Cytomegalovirus infection, lipoprotein (a), and hypercoagulability: an atherogenic link? Arterioscler Thromb Vasc Biol 17(9):1780–1785