Effects of human cytomegalovirus infection on the coagulation system

Alessandro Squizzato, Victor E. A. Gerdes, Harry R. Büller
Department of Vascular Medicine, Academic Medical Center, Amsterdam, The Netherlands

Summary
Pathophysiological mechanisms of acute vascular thrombosis are not fully understood. It has been suggested that different infectious pathogens are responsible agents of thrombotic disorders. The infection hypothesis is supported by an increasing number of reports on the interaction between acute infection and coagulation. Cytomegalovirus (CMV) is supposed to play an important role in apparently unprovoked thrombosis. We reviewed all human in *vitro* and in *vivo* studies on the influence of human CMV infection on the coagulation system, as well as all case reports of acute thrombosis during acute human CMV infection. In the published literature there is mounting evidence that human CMV may play a role in thrombotic disorders. Definitive conclusions, however, cannot be drawn, although the *in vitro* studies are convincing and offer insight in the pathogenesis.

Keywords
Infection / bacterial, viral, hypercoagulability, inflammatory mediators, endothelial cells

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**Introduction**

Acute vascular thrombosis represents a major socioeconomic challenge for its heavy burden on mortality and morbidity. Acute vascular thrombosis also represents a scientific challenge since exact pathophysiological mechanisms are incompletely understood. Different infectious pathogens have been suggested as responsible agents of thrombotic disorders. The infection hypothesis is supported by an increasing number of reports on the interaction between acute infection and coagulation. Cytomegalovirus (CMV) is postulated to play an important role in apparently unprovoked thrombosis.

The purpose of this review is to summarize the literature on the influence of human CMV infection on the coagulation system. We reviewed all human *in vitro* and *in vivo* studies as well as clinical case reports. The main findings will be highlighted and discussed after a brief initial description of CMV biology and disease. Definitive conclusions cannot be drawn, even if there is mounting evidence that CMV may play causal role in thrombotic disorders.

**CMV: relevant biological and clinical features**

CMV, or Human Herpes Virus 5, is a double-stranded enveloped DNA virus of the Herpesviridae family. The first CMV infection was described in the beginning of the previous century. Typical owl’s eye intranuclear inclusions were observed in tissues from foetuses stillborn following cytomegalic inclusion disease. In 1957, Weller named the virus CMV after the aspect of infected cells in culture (1). CMV is a typical herpes virus, with centrally located DNA surrounded by an icosahedral capsid, the tegument, and an envelope (2). Typically, after entry into target cells, the virus may remain in a stage of latency and eventually reactivate (secondary infection), particularly in case of immunodeficiency; or, alternatively, it can cause destruction of the infected cells, which is mediated by both its own cytopathogenic property and by immune response (3). Direct suppression of the immune response is probably one of several mechanisms that CMV has developed to evade cellular immune response. Humoral immune response markers against CMV are immunoglobulin (Ig) M and IgG antibodies, but whether these immunoglobulins play an important role in the defence against CMV is still unclear. The diagnosis of acute CMV infection is usually based on serology. Other diagnostic tools are the presence of pp65 antigenemia.
granulocytes from peripheral blood, viral DNA detection by polymerase chain reaction (PCR), viral mRNA detection by nucleic acid sequence-based amplification (NASBA), conventional cell culture or detection of early antigen fluorescent foci in cultures (4).

CMV infection is common worldwide, with seroprevalence rates of 40–100% (5), depending on the country, socioeconomic conditions, and the patient’s age. Infection comprises the whole lifespan of humans: it can be acquired even before birth. It is most often asymptomatic, but active CMV infection is occasionally revealed by flu-like symptoms, or mononucleosis-like syndrome, with prolonged fever, cervical lymphadenitis, and arthralgia. Although this is rare, infection may present as pneumonia, hepatitis, myocarditis, pericarditis, colitis, and haemolytic anaemia. The virus can be transmitted by intimate contact such as between mother and child by breast-feeding, between children in day care centres, by sexual contact, by blood transfusion (leucocytes), or by organ transplantation. As mentioned above, presentations of CMV disease are remarkably protean, potentially involving almost every organ system in humans. While many manifestations are encountered in conjunction with a mononucleosis-like syndrome, disease symptoms localized to a single organ has also been described (in immunocompetent hosts) (6, 7).

The involvement of the cardiovascular system has been clearly demonstrated (2). Pericarditis and myocarditis are well described by ECG, serology, culture, and PCR data that demonstrate a tissue infection during CMV acute disease (8–12). Vasculitis is also a well-documented phenomenon, occurring predominantly in the vasculature of the gastrointestinal tract where it causes colitis (13–17), the central nervous system where it causes cerebral infarction (18, 19), and in the skin where it results in petechiae, purpura papules, localized ulcers or a diffuse maculopapular eruption (20). The link between CMV and atherosclerosis is more debatable. On the one hand, the presence and level of anti-CMV antibodies are positively related to postangioplasty restenosis (21, 22), and to accelerated coronary atherosclerosis after cardiac transplantation (23). On the other hand, results from a number of in vivo and in vitro studies failed to support this hypothesis (24–36).

CMV and the coagulation system

The relation between CMV and thrombotic disorders is also a matter of debate. Severe bacterial infections, some viral infections (i.e. Dengue) and inflammation almost invariably lead to haemostatic abnormalities, ranging from insignificant laboratory changes to severe disseminated intravascular coagulation (DIC) (37). Systemic inflammation results in activation of coagulation, due to tissue factor-mediated thrombin generation, down regulation of physiological anticoagulant mechanisms, and inhibition of fibrinolysis. Pro-inflammatory cytokines usually play a central role in the differential effects on the coagulation and fibrinolysis pathways. Vice-versa, activation of the coagulation system may importantly affect inflammatory responses by direct and indirect mechanisms. Apart from the general coagulation response to inflammation associated with severe infection, specific infections may cause distinct clinical features. CMV has been associated with thrombocytopenia (38), thrombotic thrombocytopenic purpura (39), and acute arterial and venous thromboembolism (40–77).

The exact mechanism by which CMV may interfere with the haemostatic system is incompletely understood. It could be mediated only by the inflammatory response and endothelial cell activation. However, in vitro studies also suggest a direct effect of CMV on the coagulation cascade.

In vitro studies

CMV-dependent procoagulant activity was investigated both in CMV-infected cells and in isolated purified viral strains. CMV strain AD169 infected human umbilical venous endothelial cells (78–84) were usually chosen as an in vitro human model to demonstrate a procoagulant activity during a human CMV infection.

Both functional and morphologic parameters were collected and the results suggest a clear procoagulant response via several mechanisms. As detected by merocyanine 540 assay (78, 81), infection leads to cell membrane perturbation. This initial step supports a possible change of infected cells into a procoagulant state. Different clotting assays (clotting time assays and chromogenic assays with normal and plasma deficient in factors VII, X, V, and II, coagulometer cups) showed a decreased clotting time after CMV infection (78–80). In particular, a tissue factor (TF)-like activity of perturbed cell membrane was suggested (80). Moreover, von Willebrand factor (vWF) is released during CMV infection (83). A lack of a clear response of plasminogen activator inhibitor 1 (PAI-1) and urokinase like plasminogen activator (u-PA) makes a major effect on the fibrinolytic system unlikely (78).

An interaction of CMV with inflammatory responses has been suggested by modest production of interleukin (IL) 6 derived from infected endothelial cells (82) and monocytes (79). CMV infection of endothelial cells increases the expression of CD40, a cell surface receptor involved in a number of processes, such as immune response, inflammation, and the activation of endothelia (85). In particular CD40 is present on atheroma-associated cells and its ligation activates a number of processes responsible for lesion progression and plaque destabilization, such as the production of tissue factors (86). Some studies showed that CMV infection of endothelial cells results in the enhanced adherence of monocytes (MCs) and polymorphonuclear leukocytes (PMNs), but not platelets. Increased adherence was found at 24 hours post infection, especially for PMN, reflecting probably the difference in function for both cell types: PMNs are active in an acute phase, whereas MCs are acting in a later stage of the immune response (87). Enhanced PMNs adherence is probably based on increased expression of endothelial leukocyte adhesion molecule-1 (ELAM-1) secondary to autocrine IL-1 production (88).

Together, these studies on the infection of different cell types suggest activation of the coagulation system mediated by TF expression on the surface of endothelial cells, probably in combination with a changed co-expression of phospholipids on the outer cell membrane, and a lack of direct effect on fibrinolysis. Inflammatory mediators, cytokines, MCs and PMNs inflammatory cells, may act as co-factors. An important drawback to this hypothesis is the restricted capacity of AD169 CMV strain and of
other laboratory CMV strains to infect endothelial cells and leukocytes in vitro. Endothelial (both venous and arterial) cell-tropism and leucocyte-(polymorphonuclear- and monocyte-) tropism (leukotropism) are two important biological properties shared by all recent clinical isolates of human CMV. Most strains can change the genetic content and, consequently, the tropism properties of the virus after several passages in human fibroblast cultures (89). In vivo studies also demonstrated that attenuated CMV strains may reacquire endothelial cell- and leucocyte-tropism (90, 91). Nevertheless, it is still a matter of debate if in-vitro endothelial cell- and leucocyte-tropism may be good correlates of in vivo pathogenicity (92).

Intrinsic procoagulant properties of CMV were studied in two well-designed studies (93, 94). Prydzial and colleagues showed that purified CMV, strain AD169, expresses constitutively phosphatidylserine (PS)-like procoagulant activity (93). They observed a CMV-dependent decrease in the factor Xa clotting time. The assembly of a functional complex between factor Xa and the cofactor Va to form prothrombinase was dependent on the addition of CMV. These data suggested that the CMV surface, probably the envelope, contains the necessary procoagulant phospholipids for coagulation enzyme complex assembly. This may enable CMV to bypass an important physiologic regulatory mechanism for the production of thrombin.

Sutherland and colleagues confirmed these observations and demonstrated that CMV is also able to facilitate factor Xa generation from the inactive precursor factor X, but only when factor VII/VIIa and calcium are present (94). Monoclonal antibodies specific for TF, the coagulation initiator, inhibited this factor X activation and, furthermore, enabled identification of TF antigen on each virus type by flow cytometry and electron microscopy. These properties were not unique for CMV, but also present in other herpes viruses (94).

These data indicate that CMV can initiate the generation of thrombin by having the essential procoagulant phospholipids and TF activity on its surface. Unlike the normal cellular source, the viral activity is constitutive and, therefore, not restricted to sites of vascular injury. Thus, cell-independent thrombin production may be the earliest event in vascular pathology mediated by CMV.

In vivo studies
Well-designed human in vivo studies are lacking. However, some data can be extrapolated from three studies in which the relationship between CMV infection and coagulation activation was not the primary objective. Schambek and colleagues evaluated, in a retrospective study, 34 patients with previous venous thromboembolism (VTE) referred for a thrombophilia screening who had an unexplained high plasma level of factor VIII (95). CMV IgM and IgG antibodies were detected at the same frequency in the VTE group with high factor VIII levels and in the VTE control group with normal factor VIII levels. Antibody titres were modestly higher in the high factor VIII levels group (odds ratio 3.2, 95% Confidence Interval: 1–10). Based on these results, the authors suggested that an active CMV infection could trigger enhanced factor VIII synthesis or secretion. Since high factor VIII concentration is associated with an increased risk of VTE, active CMV infection might increase the risk indirectly.

Recently, 39 patients with recent kidney transplantation were studied during an acute CMV infection (96). Particularly parameters of endothelial cell damage (ED) were measured in the peripheral blood: von Willebrand factor (vWF), soluble intercellular adhesion molecule 1 (sICAM-1), soluble vascular cell adhesion molecule 1 (sVCAM-1), soluble E selectin (sE-Sel), and infected and non-infected circulating endothelial cells. The presence of infected and non-infected circulating endothelial cells, and the levels of vWF and sVCAM-1 were directly correlated with the viral infection. The increased vWF level, and the endothelial cell disturbances, can also be regarded as a procoagulant response.

The Atherosclerosis Risk in Communities (ARIC) study is a multicenter longitudinal study on the natural history and risk factors of cardiovascular disease (97). Populations from four USA communities (total participants: 15,800) were studied. The investigators collected in 300 adult residents in Washington County anti-CMV antibodies both in 1974 and between 1987–1989, and coagulation parameters between 1987 and 1989. They found a direct correlation between the presence of antibodies in 1974 and plasma levels of factor VIII activity, vWF antigen, protein C, and lipoprotein (a) in 1987–1989. An inverse association with aPTT was also observed. The relation was only detected in the longitudinal study analyses. There was no association between the presence of CMV antibodies in 1987–1989 and coagulation parameters in the same period. The authors stated that CMV infection is possibly related to atherosclerotic disease, or its manifestations, by haemostatic dysfunction and thrombosis, especially by increasing Lp(a) that subsequently reduces fibrinolysis. It is evident that the data from these three studies are insufficient to conclusively prove a role for CMV in the pathogenesis of thrombotic and/or atherosclerotic disorders.

Clinical case reports: acute infection and acute thrombosis
We identified case reports of acute thrombosis during acute CMV infection in the all-languages literature through an extensive search of the MEDLINE and EMBASE databases with terms “cytomegalovirus”, “CMV”, and “thrombosis” up to August 2004. A detailed review of the references completed the research. All cases reported in the literature of acute vascular thrombosis in immunocompetent and immunocompromised patients were collected and are summarized in tables 1 and 2 respectively (40–68).

Most cases are HIV infected patients, maybe because HIV infection itself is associated with a prothrombotic state (69–70). Another possibility is that the course of CMV infection may be more pronounced in HIV. Apparently, CMV-related thrombosis does not have a specific feature. Different organs, veins and arteries, children and adults, males and females, immunocompetent and immunocompromised patients are equally involved.

Hepatic arterial thrombosis (HAT) is an unusual site for thrombosis, which may occur after a liver transplantation (71). It is one of the principal causes of morbidity and graft loss following liver transplantation, especially in paediatric patients (72). There are several risk factors for the development of HAT. Technical aspects of the arterial anastomosis are important particularly for early thrombosis, but also a variety of conditions such as
Table 1: Case reports of acute thrombosis during acute CMV infection in immunocompetent patients reported in the literature.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Diagnosis of CMV infection</th>
<th>Type of thrombosis</th>
<th>Diagnosis of thrombosis</th>
<th>Thrombosis risk factors</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4 months</td>
<td>F</td>
<td>Serology + viruria</td>
<td>Portal vein</td>
<td>Doppler ultrasonography</td>
<td>Low pr. C and pr. S</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>31</td>
<td>F</td>
<td>Serology</td>
<td>Portal vein</td>
<td>Doppler ultrasonography</td>
<td>No</td>
<td>41</td>
</tr>
<tr>
<td>3</td>
<td>35</td>
<td>M</td>
<td>Serology + viruria</td>
<td>Superior mesenteric vein; femoropopliteal DVT</td>
<td>Doppler ultrasonography; abdominal CT</td>
<td>aPL +</td>
<td>42</td>
</tr>
<tr>
<td>4</td>
<td>31</td>
<td>F</td>
<td>Serology</td>
<td>Portal vein; Superior mesenteric vein</td>
<td>Doppler ultrasonography; abdominal CT</td>
<td>No</td>
<td>43</td>
</tr>
<tr>
<td>5</td>
<td>29</td>
<td>M</td>
<td>Histology</td>
<td>Mesenteric vein; venulitis in the small intestine</td>
<td>Exploratory laparotomy</td>
<td>No</td>
<td>44</td>
</tr>
<tr>
<td>6</td>
<td>30</td>
<td>M</td>
<td>Serological</td>
<td>Acute inferior myocardial infarction</td>
<td>ECG and echocardiogram</td>
<td>Not reported</td>
<td>45</td>
</tr>
<tr>
<td>7</td>
<td>32</td>
<td>F</td>
<td>Serology</td>
<td>Iliac vein</td>
<td>Abdominal CT; femoral venography</td>
<td>IgM anticardiolipin antibodies +</td>
<td>46</td>
</tr>
<tr>
<td>8</td>
<td>50</td>
<td>M</td>
<td>Inclusion in specimen</td>
<td>Extensive mesenteric artery and vein</td>
<td>Abdominal CT; laparotomy</td>
<td>No</td>
<td>47</td>
</tr>
<tr>
<td>9</td>
<td>Neonatal</td>
<td>F</td>
<td>PCR in organ specimens</td>
<td>Aortic arch</td>
<td>Echocardiography</td>
<td>No</td>
<td>48</td>
</tr>
<tr>
<td>10</td>
<td>31</td>
<td>F</td>
<td>Serology + viremia</td>
<td>Portal vein</td>
<td>Doppler ultrasonography</td>
<td>No</td>
<td>49</td>
</tr>
<tr>
<td>11</td>
<td>42</td>
<td>M</td>
<td>Serological</td>
<td>Mesenteric superior vein</td>
<td>Abdominal CT and eco-doppler</td>
<td>No</td>
<td>50</td>
</tr>
<tr>
<td>12</td>
<td>38</td>
<td>F</td>
<td>Inclusion in specimen</td>
<td>Iliac vein; PE</td>
<td>Doppler ultrasonography; pulmonary scintigraphy</td>
<td>No</td>
<td>51</td>
</tr>
<tr>
<td>13</td>
<td>32</td>
<td>F</td>
<td>Serology and viremia</td>
<td>Femoropopliteal DVT; PE; internal jugular vein</td>
<td>Doppler ultrasonography; pulmonary-cervical CT</td>
<td>Factor V Leiden (heterozygous)</td>
<td>51</td>
</tr>
<tr>
<td>14</td>
<td>40</td>
<td>M</td>
<td>Viremia and antigenemia</td>
<td>Sup. mesenteric vein to portal and splenic vein</td>
<td>Histopathological on surgical sample</td>
<td>No</td>
<td>52</td>
</tr>
<tr>
<td>15</td>
<td>35</td>
<td>M</td>
<td>Serology</td>
<td>PE</td>
<td>Pulmonary scintigraphy</td>
<td>Not reported</td>
<td>53</td>
</tr>
</tbody>
</table>

Pr. C, protein C; pr. S, protein S; aPL, antiphospholipids; DVT, deep venous thrombosis; PE, pulmonary embolism

Discussion

The reported studies indicate that CMV may be a relevant factor in thrombotic disease. There are a number of convincing in vitro studies in which procoagulant effects were observed, either by the virus itself, or by a procoagulant influence on endothelial cells or monocytes. However, the in vivo data are less clear. A number of case reports have been published, and three studies in which secondary analyses showed possible procoagulant influences of CMV. We conclude that it is likely that CMV is involved in the pathogenesis of thrombosis, but whether this is only in certain extreme conditions like organ transplantation with immunosuppression, or whether CMV may be responsible for a proportion of venous or arterial complications in the general population, needs to be elucidated.

Different mechanisms are probably involved in the pathogenesis of CMV-induced thrombosis. Endothelial cells turn in a procoagulant state as CMV directly infects endothelium and causes membrane perturbation. Subsequently, altered surface protein expression may also cause TF exposure to the blood stream, and increased leukocyte adhesion, responsible for a local inflamma-

low donor/recipient age ratio, immunologic factors, clotting abnormalities, tobacco use, and infections (73). First, Madalosso and colleagues (74) showed a positive association between the uses of a CMV-seropositive donor liver in a seronegative recipient and the incidence of HAT within the first 30 days (conventional cut–off time to distinguish between early and late HAT). Recently, 11 cases of late HAT were published: 5 (45.5%) of them had a CMV infection, in contrast with 56 out of 382 patients (14.7%) of the control group (75). In another study, the combination of a CMV positive allograft and a CMV negative recipient was a significant risk factor for developing early HAT and the combination of recipient CMV negative and donor CMV negative was a significant risk factor for late HAT (76).

Vascular access dysfunction is the main cause of morbidity and hospitalisation in the haemodialysis population, and thrombosis is the leading cause for arteriovenous fistula (AVF) failure. Recent serological data suggest that CMV infection is also involved and represent an independent risk factor for haemodialysis access thrombosis (77).
Intrinsic CMV procoagulant properties, which are probably directly acquired during envelope constitution from the modified endothelial cell membrane, start and/or amplify haemostatic imbalance. Additionally, TF is added by CMV-infected monocytes involved in the inflammatory response (Scheme 1).

Theoretically, other viruses may have a procoagulant effect by the same mechanisms. However, though endothelial cells can

Table 2: Case reports of acute thrombosis during acute CMV infection in immunocompromised patients reported in the literature.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis of CMV infection</th>
<th>Type of thrombosis</th>
<th>Diagnosis of thrombosis</th>
<th>Immunodeficient state</th>
<th>Thrombosis risk factors</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Young F</td>
<td>Post-mortem</td>
<td>Non bacterial thrombotic endocarditis</td>
<td>Post-mortem</td>
<td>Kaposi sarcoma (probably HIV-related)</td>
<td>Not reported</td>
<td></td>
<td>54</td>
</tr>
<tr>
<td>2</td>
<td>32 M</td>
<td>Post-mortem</td>
<td>PE</td>
<td>Post-mortem</td>
<td>HIV</td>
<td>Immobilization</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>34 M</td>
<td>Histology on surgical specimen</td>
<td>Septic thrombophlebitis</td>
<td>Biopsy specimen</td>
<td>HIV and Kaposi sarcoma</td>
<td>Not reported</td>
<td></td>
<td>56</td>
</tr>
<tr>
<td>4</td>
<td>36 F</td>
<td>Post-mortem</td>
<td>Coronary arterial thrombosis</td>
<td>Autopsy</td>
<td>Heart transplantation</td>
<td>Not reported</td>
<td></td>
<td>57</td>
</tr>
<tr>
<td>5</td>
<td>23 F</td>
<td>Serology and viruria</td>
<td>Cerebral venous thrombosis</td>
<td>Digitalised angiograms</td>
<td>HIV</td>
<td>Not reported</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>58 M</td>
<td>Culture of BAL</td>
<td>Renal arterial thrombosis and DIC</td>
<td>Duplex ultrasonography</td>
<td>Renal transplantation</td>
<td>Not reported</td>
<td>59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7–12</td>
<td>42–57 M</td>
<td>Histology and ex juvantibus</td>
<td>PE and DVT</td>
<td>Phlebography vent./perf. scan</td>
<td>HIV</td>
<td>Not reported</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>28 M</td>
<td>Biopsy-immunohistochemical staining</td>
<td>Digital infarct</td>
<td>Biopsy specimen</td>
<td>HIV</td>
<td>Low pr. C and apl +</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>38 M</td>
<td>Blood culture and biopsy-immunohistochemical staining</td>
<td>Digital infarct</td>
<td>Biopsy specimen</td>
<td>HIV</td>
<td>Not reported</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>64 M</td>
<td>CMV retinitis</td>
<td>Retinal vein occlusion</td>
<td>Fluorescein angiography</td>
<td>HIV</td>
<td>Not reported</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>26 M</td>
<td>CMV retinitis</td>
<td>Branch retinal artery and vein occlusion</td>
<td>Fluorescein angiography</td>
<td>HIV</td>
<td>Not reported</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>44 M</td>
<td>Histology</td>
<td>Middle and left colic veins and ischemic colitis</td>
<td>Histopathological on surgical specimen</td>
<td>Renal transplantation</td>
<td>Not reported</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>57 M</td>
<td>Histopathological on oesophagus specimen</td>
<td>Bilateral internal jugular veins</td>
<td>Doppler ultrasound</td>
<td>HIV</td>
<td>No thrombophilia</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>37 M</td>
<td>CMV retinitis</td>
<td>Central retinal vein occlusion</td>
<td>Fluorescein angiography</td>
<td>HIV</td>
<td>Low pr. C and pr. S</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>40 M</td>
<td>Serology</td>
<td>Femoropopliteal DVT and PE</td>
<td>Duplex ultrasonography and thorax spiral CT</td>
<td>Prednisone and cyclophosphamide</td>
<td>Not reported</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>74 M</td>
<td>Histopathological</td>
<td>Popliteal DVT and PE</td>
<td>Duplex ultrasonography and pulmonary scintigraphy</td>
<td>Prednisone and cyclophosphamide</td>
<td>Not reported</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>48 F</td>
<td>Serology</td>
<td>Bilateral femoral DVT</td>
<td>Duplex ultrasonography</td>
<td>Prednisone and cyclophosphamide</td>
<td>Not reported</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>23–29</td>
<td>36–60</td>
<td>7M-1F</td>
<td>DNA load by PCR</td>
<td>DVT and/or PE</td>
<td>Doppler ultrasonography and pulmonary scintigraphy</td>
<td>Renal transplantation</td>
<td>Anticardiolipin antibodies in 3 cases</td>
<td>68</td>
</tr>
</tbody>
</table>

Pr. C, protein C; pr. S, protein S; apl, antiphospholipids; DVT, deep venous thrombosis; PE, pulmonary embolism.
be directly infected by different viruses (Table 3) (37, 98–102), a procoagulant activity has only been reported for CMV, Herpes simplex virus type 1 (HSV-1) and 2 (HSV-2), Varicella Zoster Virus (VZV), and HIV infection. In vitro experiments showed that HSV-1, HSV-2, Influenza A and B viruses, ParainfluenzaVirus 1, Respiratory Syncytial Virus, and Adenovirus might have a procoagulant effect as well (80, 94). It is only for HIV and CMV that a substantial number of published case reports of patients with these infections and thrombosis can be found. We conclude that it is unclear whether the procoagulant effect is specific for CMV.

CMV has been reported in association with both arterial and venous thrombosis. Pathophysiological mechanisms of arterial and venous thrombosis differ. An arterial thrombus is mainly formed by platelets, and rupture of an atherosclerotic plaque is the underlying pathophysiologic mechanism in most of the cases. Major risk factors are smoking, hypertension, dyslipidemia, and diabetes. On the contrary, venous thrombosis is mainly formed by fibrin and major risk factors are immobilisation, surgery, pregnancy and oral contraceptives, cancer and procoagulant mutations. CMV probably plays a different role in inducing arterial or venous thrombosis. CMV could be involved in two different stages of arterial disease. First, biological and epidemiological data indicate that chronic CMV infection of endothelial cells and the subsequent cell response (‘CMV endothelitis’) may play a role in the pathogenesis of atherosclerosis, even if at this moment the relative clinical importance is unclear (103). Secondly, an acute cardiovascular event could be the result of the hypothesized property of CMV to lead to instability of the atherosclerotic plaque and to induce a procoagulant state during an acute infection or reactivation (104, 105). Whether CMV is a relevant factor or an innocent bystander remains to be solved. The relation between CMV and atherosclerosis has been reviewed elsewhere (23, 34, 106, 107).

Indeed, there may be clinical consequences if CMV is demonstrated as an important pathogen in arterial and venous thrombosis. Drug prophylaxis or vaccination, nowadays not available, may become attractive tools to prevent thrombosis. Recently also statins have been demonstrated to limit CMV infection in humans endothelial cells, inhibiting viral antigen expression, DNA synthesis, and viral particle production (108).

Since sound evidence is lacking, well-designed prospective studies are therefore needed to confirm in vitro findings, elucidate the pathophysiologic mechanisms, and define if CMV primary or secondary infection really is an important risk factor for arterial and venous thrombosis in immunocompetent and immunocompromised patients; if so, the value of anti-viral therapy in certain patient groups should be assessed, for instance, transplantation patients, as prophylaxis for thrombosis.

In conclusion, there is mounting evidence that CMV may play a role in thrombotic disorders. Although the in vitro studies are convincing and offer insight in the pathogenesis, the in vivo studies do not convincingly prove a causal role for CMV in arterial or venous thrombosis. Definitive conclusions cannot be drawn without well-designed prospective clinical studies evaluating the role of CMV as risk factor for venous and arterial thrombosis.

Table 3: Viruses that can infect endothelial cells.

<table>
<thead>
<tr>
<th>Virus</th>
<th>Virus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenovirus</td>
<td>Influenza A virus</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Influenza B virus</td>
</tr>
<tr>
<td>Echovirus</td>
<td>Measles virus</td>
</tr>
<tr>
<td>Filoviruses</td>
<td>Mumps virus</td>
</tr>
<tr>
<td>Hantaviruses</td>
<td>ParainfluenzaVirus 1</td>
</tr>
<tr>
<td>Herpes simplex virus type 1</td>
<td>Poliovirus</td>
</tr>
<tr>
<td>Herpes simplex virus type 2</td>
<td>Respiratory Syncytial Virus</td>
</tr>
<tr>
<td>Human ImmunodeficiencyVirus</td>
<td>Varicella Zoster Virus</td>
</tr>
<tr>
<td>Human T Cell LymphotropicVirus</td>
<td>type 1</td>
</tr>
</tbody>
</table>

References
Squizzato, et al.: Effects of CMV infection on the coagulation system


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