A Case Report and Literature Review of Portal Vein Thrombosis Associated with Cytomegalovirus Infection in Immunocompetent Patients

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We describe a young man with acute portal vein thrombosis (PVT) and cytomegalovirus (CMV) infection, and we review the literature regarding the association between PVT and CMV in immunocompetent patients. Published data suggest that CMV hepatitis and, possibly, other types of acute viral hepatitis could be a local risk factor for acute PVT.

Several local and systemic factors are involved in the pathogenesis of acute portal vein thrombosis (PVT). In particular, intra-abdominal inflammatory processes, such as acute and chronic pancreatitis, cholecystitis, and appendicitis, are well recognized risk factors of PVT [1]. Neither acute hepatitis nor acute cytomegalovirus (CMV) infection—which is both a hypothesized systemic procoagulant risk factor and a certain cause of viral hepatitis—is usually reported as a potential risk factor for PVT [1–3]. We describe a young immunocompetent man who experienced prompt resolution of an asymptomatic acute PVT in a highly likely case of CMV infection and review the available evidence of the natural history of acute CMV-mediated PVT.

**Case report.** A 34-year-old white man with an echographic diagnosis of PVT was admitted to a tertiary care hospital (Ospedale di Circolo, Varese, Italy) on 26 March 2005. His past medical, family, and social history was unremarkable, apart from a spontaneous pneumothorax at the age of 13 years. In the 2 weeks prior to his admission to the hospital, he was unsuccessfully treated with antibiotic therapy (ampicillin and erythromycin) by a general practitioner for a persistent fever unsuccessfully treated with antibiotic therapy (ampicillin and erythromycin) by a general practitioner for a persistent fever.

At admission, the patient was asymptomatic; in particular, he did not report any abdominal symptoms. He was still receiving antibiotic therapy and was not receiving any additional medication. On physical examination, his blood pressure was 140/90 mm Hg, he had a regular pulse rate of 96 beats/min, his body temperature was 38.3°C, and his blood oxygen saturation level on breathing air was 97%. Abdominal palpation revealed a mild enlargement of the liver and of the spleen during deep inspiration. Serum testing revealed a mild elevation of aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase levels (57 U/L, 94 U/L, and 866 U/L, respectively) and a marked elevation of the D-dimer level (1010 μg/L; cutoff value, <200 μg/L). Other laboratory test results were normal, except for a relative lymphocytosis (61.3%). Both electrocardiogram and chest radiograph findings were normal. Urine and blood culture results were negative for bacterial growth.

An urgent computed tomographic scan of the abdomen using intravenous iodine contrast medium confirmed a nonenhancing filling defect within the lumen of the left branch of the portal vein. Organ masses, which are possible local causes of portal vein thrombosis, were excluded, apart from 1-cm-diameter lymphonodes located at the hepatic ileum. The patient was given a full therapeutic dose of low molecular weight heparin, enoxaparin (8000 IU twice daily), and, few days later, 5 mg of warfarin. He continued to receive warfarin, with a target international normalized ratio of 2.5, for the following 6 months.

During the patient’s hospitalization, an extensive serological screening was performed with the aim to identify any possible viral cause of hepatitis and persistent fever; test results for hepatitis B surface antigen, antihepatitis B core antigen IgG, hepatitis C virus IgG, hepatitis A virus total immunoglobulin and IgM, Toxoplasma gondii IgM, Epstein-Barr virus anti–viral capsid antigen IgM, HIV-1 and -2 total IgG, and parvovirus B19 antiantigen recombinant VP2 IgM antibodies were all negative. Rubella IgM and herpes simplex 1 and 2 IgM index test results were not conclusive. The CMV IgM index value was 2.5 (cutoff value, >1.1), the IgG antibody level was 1.3 UI/mL (cutoff value,
Table 1. Published cases of acute portal vein thrombosis (PVT) associated with cytomegalovirus (CMV) infection.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age*/sex</th>
<th>Method of diagnosis of CMV infection</th>
<th>Extension of PVT</th>
<th>Duration of radiologic follow-up (method): outcome</th>
<th>Abnormal AST and/or ALT serum levels</th>
<th>Abdominal symptoms</th>
<th>Associated VTE risk factors</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 4 months/F</td>
<td>Serologic testing, viruria</td>
<td>Not specified</td>
<td>4 months (ultrasonography): portal vein cavernoma</td>
<td>AST, 125 IU/L; ALT, 145 IU/L</td>
<td>Not applicable</td>
<td>Low protein C and protein S levels</td>
<td>[7]</td>
<td></td>
</tr>
<tr>
<td>2 31/F</td>
<td>Serologic testing</td>
<td>Partial thrombosis of the right branch</td>
<td>12 days (ultrasonography): complete resolution without antithrombotic therapy</td>
<td>AST, 3.23 µKat/L; ALT, 4.75 µKat/L</td>
<td>Pain in the right upper abdominal quadrant with nausea</td>
<td>Oral contraceptive pill use</td>
<td>[8]</td>
<td></td>
</tr>
<tr>
<td>3 31/F</td>
<td>Serologic testing</td>
<td>Partial thrombosis of the trunk, the left and right branches, and the superior mesenteric vein</td>
<td>2 months (ultrasonography): complete disappearance</td>
<td>AST, 140 IU/L; ALT, 240 IU/L</td>
<td>Pain in the right upper abdominal quadrant</td>
<td>Oral contraceptive pill use</td>
<td>[9]</td>
<td></td>
</tr>
<tr>
<td>4 31/F</td>
<td>Serologic testing, viremia</td>
<td>Partial thrombosis of the left branch</td>
<td>11 months (CT): complete resolution, but reduced blood flow velocity</td>
<td>AST, 51 IU/L</td>
<td>No abdominal pain</td>
<td>Oral contraceptive pill use</td>
<td>[10]</td>
<td></td>
</tr>
<tr>
<td>5 40/M</td>
<td>Viremia, antigenemia</td>
<td>Not specified; superior mesenteric vein and splenic vein</td>
<td>2 months (ultrasonography): complete resolution</td>
<td>AST, 100 IU/L; ALT, 218 IU/L</td>
<td>Acute diffuse abdominal pain with diarrhea and vomiting</td>
<td>None</td>
<td>[11]</td>
<td></td>
</tr>
<tr>
<td>6 37/M</td>
<td>Serologic testing, CMV-DNA</td>
<td>Left branch</td>
<td>4 months (ultrasonography): complete recanalization</td>
<td>AST, 104 IU/L; ALT, 162 IU/L</td>
<td>Upper abdominal pain increased with deep inspiration</td>
<td>None</td>
<td>[12]</td>
<td></td>
</tr>
<tr>
<td>7 38/M</td>
<td>Serologic testing</td>
<td>Partial thrombosis of the trunk, the left and right branches, and the superior mesenteric vein</td>
<td>3 months (CT): complete recanalization</td>
<td>ALT, 53 IU/L</td>
<td>Acute diffuse abdominal pain, preceded for 3 weeks by frequent episodes of epigastric pain and vomiting</td>
<td>Factor II G20210 heterozygosis</td>
<td>[13]</td>
<td></td>
</tr>
<tr>
<td>8 33/M</td>
<td>Serologic testing</td>
<td>Complete thrombosis of the right branch and partial thrombosis of the left branch, the trunk, and the superior mesenteric vein</td>
<td>3 months (CT): incomplete thrombosis of the right portal branch</td>
<td>ALT, 69 IU/L</td>
<td>Intense abdominal pain</td>
<td>Factor II G20210 heterozygosis</td>
<td>[13]</td>
<td></td>
</tr>
<tr>
<td>9 36/F</td>
<td>Serologic testing, CMV-DNA</td>
<td>Portal trunk, splenic vein, and right hepatic vein</td>
<td>5 months (ultrasonography): persistent obstruction with cavernoma</td>
<td>AST, 76 IU/L; ALT, 111 IU/L</td>
<td>Abdominal pain</td>
<td>Oral estrogens</td>
<td>[14]</td>
<td></td>
</tr>
<tr>
<td>10 29/M</td>
<td>Antigenemia, CMV-DNA</td>
<td>Partial thrombosis of the portal trunk</td>
<td>3 months (ultrasonography): complete recanalization</td>
<td>AST, 350 IU/L</td>
<td>No abdominal pain</td>
<td>None</td>
<td>[15]</td>
<td></td>
</tr>
<tr>
<td>11 34/M</td>
<td>Serologic testing</td>
<td>Partial thrombosis of the left branch</td>
<td>10 days: complete recanalization</td>
<td>AST, 479 IU/L; ALT, 164 IU/L</td>
<td>No abdominal pain</td>
<td>None</td>
<td>Present case</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. ALT, alanine aminotransferase; AST, aspartate aminotransferase; VTE, venous thromboembolism.

* Age is in years, unless otherwise indicated.
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...aspartate aminotransferase levels remained increased (164 and 479 IU/dL, respectively). The conclusive diagnosis was acute PVT associated with a probable acute CMV infection, because no other obvious causes could explain clinical and laboratory data.

Extensive screening for thrombophilia was performed after discontinuation of oral anticoagulation therapy—that is, 8 months after the diagnosis of thrombosis. The results of this screening were negative. Wild-type factor II and V genes were present, protein C resistance was absent, a screening test for antithrombin activity was within the reference range (20–29 IU/L). The results of this procedure—dilute Russell’s viper venom time—and fibrinogen level was 102%, factor VIII activity was 150% (reference range, 50%–200%), homocysteine level was 9.7 μmol/L, and normal levels of IgM and IgG anti–glycoprotein 1 antibodies, as well as negative lupus anticoagulant (activated thromboplastin time and dilute Russell’s viper venom time), were present. At that time, aspartate aminotransferase and alanine aminotransferase levels were within the reference range (20–29 IU/L). The results of an HIV test were negative.

Discussion. Venous thromboembolism is a disease with multiple causes, often involving acquired or environmental risk factors, as well as a genetic predisposition [4]. As with PVT, single or multiple prothrombotic disorders are frequently associated with local precipitating factors, such as cirrhosis, cancer, or local inflammation [2]. In our patient, it is likely that both a systemic procoagulant state and local inflammation coexisted.

Acute infections are associated with a transient increased risk of venous thromboembolic events [5]. In particular, some viral infections almost invariably lead to hemostatic abnormalities that range from insignificant laboratory changes to severe disseminated intravascular coagulation [6]. A direct infection of endothelial cells and systemic inflammation lead to an activation of coagulation due to tissue factor-mediated thrombin generation, down-regulation of physiological anticoagulant mechanism, and inhibition of fibrinolysis [3]. In vitro studies indicate that CMV has a procoagulant effect: endothelial cells turn in a procoagulant state as CMV directly infects endothelium and causes membrane perturbation. Intrinsic CMV procoagulant properties start and/or amplify the hemostatic imbalance [3].

Furthermore, as in other acute viral infections, systemic inflammatory response syndrome and inflammatory changes in the surrounding tissues could be associated with viral acute hepatitis; propagation of acute liver inflammation to the endothelium of the portal vein system by contiguity could activate the coagulation system and increase the risk of PVT. To further support our hypothesis that acute viral hepatitis is a relevant pathogenetic factor in developing acute PVT and, in particular, in developing acute CMV-mediated PVT, we performed an extensive literature search of the Embase and Medline databases for articles published up to May 2006, to correctly describe the natural history of acute CMV-mediated PVT. No language restrictions were applied, and reference lists of all included studies were manually searched for other potential eligible studies. Our search results revealed that no case-control or cohort studies of acute CMV-mediated PVT have been published. We identified only 10 published case reports, all of which involved immunocompetent patients, 1 of whom was an infant [7–15] (table 1). Including our case, adult patients had a mean age of 34 years, and 6 patients were male (60%). Three patients (30%) did not complain of abdominal pain. Known venous thromboembolic risk factors were absent in 4 patients (40%). Eight patients (80%) experienced a complete recanalization of the portal vein that was evident at the radiologic follow-up, which was performed a median of 3 months after the PVT. Two patients (20%) experienced a complete resolution of PVT in <12 days. All 11 patients (100%) had elevated aspartate aminotransferase and/or alanine aminotransferase serum levels.

Why is viral hepatitis not usually reported as a cause of acute PVT? Published data suggest that a rapid resolution of the thrombus can occur, even without anticoagulation therapy [8]. This does not occur in more usual sites of venous thrombosis: 38.8% of patients with a deep venous thrombosis of the lower limbs experienced resolution of the thrombus after 6 months of anticoagulation therapy [16]. Moreover, mild symptomatic or asymptomatic clinical presentation can occur: 30% of acute PVT cases were detected accidentally, because patients did not complain of any abdominal pain. In our patient, PVT was completely asymptomatic; it was discovered inadvertently by ultrasonography, and it resolved completely after 10 days of antithrombotic therapy.

In conclusion, our case report reinforces the available evidence that suggests that, at the very least, acute CMV hepatitis—and, possibly, acute viral hepatitis—should be added to the list of risk factors of acute PVT. As well, these conditions should be routinely investigated in etiological clinical studies to definitively assess their causal role in acute PVT in immunocompetent patients.

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References