Spontaneous splenic rupture in primary cytomegalovirus infection

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∫ Résumé

Rupture spontanée de rate lors d’une primo-infection à cytomegalovirus

Introduction > La rupture de rate est une complication exceptionnelle de la primo-infection à cytomegalovirus (CMV).
Observations > Nous rapportons 2 cas de rupture spontanée de rate au cours d’une primo-infection à CMV chez des sujets immunocompétents. Dans un cas une profonde anémie par carence martiale était présente, et dans le second, un déficit en pyruvate kinase a été mis en évidence. Les 2 cas furent traités de façon conservatrice avec succès.
Discussion > Neuf autres cas publiés dans la littérature médicale sont également revus. Ils ne permettent pas de mettre en évidence de facteurs de risque particuliers pour cette complication.

∫ Summary

Introduction > Spontaneous splenic rupture is a rare occurrence in primary cytomegalovirus infection.
Cases > We report two cases of spontaneous rupture of the spleen associated with primary cytomegalovirus infection in young immunocompetent adults. One patient had iron deficiency anemia, and the other a pyruvate kinase deficiency. Nonoperative management was successful in both cases.
Discussion > Nine other cases identified by a search of the medical literature are also reviewed. These cases do not show evidence of any particular risk factor.

Spontaneous rupture of a previously normal spleen occurs rarely in infectious disease and has been reported mainly in malaria and infectious endocarditis and mononucleosis. Our aim in presenting these two cases and reviewing other documented cases in the literature was to identify potential risk factors for splenic rupture in primary CMV infection and assess current management of this potentially life-threatening complication of an otherwise benign disease.
Cases

Case 1
A 22 year-old woman was admitted with acute left upper quadrant abdominal pain. The only notable item in her medical history was iron deficiency anemia during pregnancy, three years previously. Febrile pharyngitis two weeks before admission had been treated with prednisolone and cefpodoxime. She complained of fatigue but reported no recent trauma. Pulse rate, blood pressure and temperature were normal at admission. Inspiration was limited by pain. Abdominal examination revealed tender palpable splenomegaly, without guarding. The patient was profoundly anemic (hemoglobin [Hb] level of 53 g/L), with a microcytic picture indicative of iron deficiency (serum ferritin 2 μg/L [N: 5-150]) and normal platelet and leukocyte counts. Values for liver function tests were initially normal, but subsequently quintupled (AST and ALT), concomitant with the development of lymphocytosis, for which 10% of the cells were atypical (large hyperbasophilic lymphocytes). Primary CMV infection was confirmed by an initial serological pattern of positive IgM and negative IgG anti-CMV antibodies with subsequent IgG seroconversion, positive whole-blood PCR, positive pp65 antigenemia, and positive viruria. IgM anti-Epstein Barr viral capsid antigen was also present, but further investigations (whole-blood PCR, tests for IgG anti-VCA and IgG anti-EBNA) ruled out EBV-induced infectious mononucleosis. Tests for antibodies against HIV and viral hepatitis A, B, C were (and remained) negative. Autoantibody screening was negative apart from a low titer of IgA anti-gliadin antibodies. Gastroscopy to investigate the anemia showed erosive gastritis. Gastric and duodenal biopsies ruled out glandular or villous atrophy. Abdominal ultrasonography confirmed splenomegaly and abdominal computed tomography (CT) scanning revealed multiple splenic contusions and/or infarcts (the largest measuring 4 by 2.5 cm) (figure 1) with moderate peritoneal effusion. The final diagnosis was spontaneous splenic rupture complicating primary CMV infection. In view of the patient’s continuing hemodynamic stability, we decided on conservative management and continued close monitoring, initially in the intensive care unit. Her profound anemia was well tolerated and thus appeared to have preceded the splenic rupture, but she received 4 units of packed red blood cells, iron supplements, and a proton pump inhibitor. After a period of prolonged bed-rest she was discharged on the 15th day post-admission. At follow-up six months later she was found to be clinically well with no palpable splenomegaly, a Hb level of 150 g/L, and a normal abdominal ultrasound.

Case 2
A 29 year-old man with a past history of migraine and testicular torsion was hospitalized with progressive pain in the upper quadrant of the abdomen radiating to the left scapula. He reported no recent trauma, but had noticed red urine once a few days before admission. In addition to tender splenomegaly, he had a low-grade fever (37.8°C); pulse rate and blood pressure were normal. The initial complete blood count showed: Hb 133 g/L, platelets 143 x 10^9/L, lymphocytes 2.2 x 10^9/L and neutrophils 2.3 x 10^9/L. On Day 12 lymphocytosis was noted (5.1 x 10^9/L), with 10% of the cells atypical; AST and ALT values tripled. Serological investigations were consistent with primary CMV infection, with positive IgM anti-CMV, pp65 antigenemia, and whole-blood PCR. The patient was seronegative for HIV, EBV, and viral hepatitis. Other findings consistent with hemolysis included reticulocytosis (140 x 10^9/L), decreased haptoglobin, lactate dehydrogenase levels three times higher than normal, and an elevated free bilirubin concentration (19 mg/L). Subsequent laboratory investigations showed a pyruvate kinase deficiency. Ultrasonography showed homogeneous splenomegaly (15 cm) and gallstones in an otherwise normal gall-bladder. CT scanning confirmed the splenomegaly and revealed a partial posterior rupture, associated with slight peritoneal effusion. Homogeneous hepatomegaly was also noted. Conservative treatment involved initial close monitoring and then complete rest for a month. Full recovery followed.

Discussion
Spontaneous splenic rupture is a rare complication of primary CMV infection. To identify possible risk factors and to clarify management guidelines, we conducted a PubMed search using the key words “cytomegalovirus”, “spleen rupture” and “spleen hematoma” and reviewed the major series of primary
CMV infection in immunocompetent patients published in English and in French. We found only eleven cases, including our own, of spontaneous splenic rupture or subcapsular hematoma during primary CMV infection (table I). Two cases of “isolated painful splenomegaly suggesting impending rupture” [1-7] were excluded because insufficiently documented. It is, however, likely that many cases of splenic rupture in primary CMV infection are unreported. Additionally, since false-positive EBV serology is frequent in CMV infection, as in our first case, it may well be that some of the published cases of “spontaneous splenic rupture in infectious mononucleosis” actually concern primary CMV infection.

The term “splenic rupture” may be somewhat misleading, since splenic infarction, subcapsular hematoma, and frank rupture may best described as events along a single continuum [7]. There is also a decided lack of certainty in labeling splenic rupture as “spontaneous” or ascribing it to a minor unnoticed trauma [8]. In 4 of 10 cases [2-5] the splenic lesion was actually a subcapsular hematoma; the remainder had total or partial splenic rupture. Hemoperitoneum was documented in 7 cases [1, 3, 6, 7, 9, 10], including one of ours. This condition affects young adults (mean age: 30, range: 22-43) with a male/female ratio of 2.7/1. All reported cases involve immunocompetent adults, which suggests that immune deficiency is not a risk factor for splenic rupture in primary CMV infection. A possible predisposing factor was identified in two cases. One had a history of malaria, but there was no information about disease activity at the time of the CMV infection. One patient (Case 2 above) had pyruvate kinase deficiency, which can cause chronic congestive splenomegaly. Thus chronic hemolysis and infection leading to splenic enlargement may both be risk factors for spontaneous splenic rupture in primary CMV infection. Furthermore, minor abdominal trauma as a possible precipitant cannot be ruled out.

### Table I

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sex/Age</th>
<th>Comorbidity</th>
<th>Spleen lesions</th>
<th>Management</th>
<th>CMV diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horwitz, 1986 [1]</td>
<td>M/38</td>
<td>Malaria</td>
<td>Complete rupture Hemoperitoneum</td>
<td>Splenectomy</td>
<td>IgM</td>
</tr>
<tr>
<td>Losada, 1997 [5]</td>
<td>F/30</td>
<td>None</td>
<td>Subcapsular hematoma</td>
<td>Nonoperative management</td>
<td>IgM Viruria</td>
</tr>
<tr>
<td>Alliot, 2001 [7]</td>
<td>F/43</td>
<td>None</td>
<td>Splenic rupture Hemoperitoneum</td>
<td>Splenectomy</td>
<td>IgM Positive blood PCR Positive spleen immunostaining</td>
</tr>
<tr>
<td>Duarte, 2003 [8]</td>
<td>M/24</td>
<td>None</td>
<td>Splenic rupture Hemoperitoneum</td>
<td>Splenectomy</td>
<td>IgM Positive spleen PCR</td>
</tr>
<tr>
<td>Gorgone, 2005 [9]</td>
<td>M/26</td>
<td>None</td>
<td>Splenic rupture Splenic infarction Hemoperitoneum</td>
<td>Splenectomy</td>
<td>IgM</td>
</tr>
<tr>
<td>Case 1</td>
<td>F/22</td>
<td>Profound iron deficiency anemia</td>
<td>Hemoperitoneum Multiple splenic contusions and/or infarcts</td>
<td>Nonoperative management</td>
<td>IgM, seroconversion pp65 antigenemia, Viruria Positive blood PCR</td>
</tr>
<tr>
<td>Case 2</td>
<td>M/29</td>
<td>Pyruvate kinase deficiency</td>
<td>Partial splenic rupture</td>
<td>Nonoperative management</td>
<td>IgM pp65 antigenemia Positive blood PCR</td>
</tr>
</tbody>
</table>

F : female; IgM: immunoglobulin M antibody against cytomegalovirus; M: male; PCR: polymerase chain reaction.
The management of these spontaneous splenic lesions has changed over the past decade. Splenectomy remains the standard treatment for hemodynamically unstable patients [8]. It is associated, however, with many potential postoperative complications (hemorrhage, subphrenic abscess, fistula, and pulmonary embolism) and with an increased long-term risk of severe bacterial infection, principally from Streptococcus pneumoniae, Neisseria meningitidis and Haemophilus influenzae, although vaccines now afford partial protection against these three. Thus recent reports have advocated nonoperative management of traumatic and spontaneous splenic rupture. Schuler et al. [8] described 17 patients (from 40 personal or published cases) so treated after spontaneous rupture of the spleen during infectious mononucleosis. Five required early-rescue splenectomy, and another a late splenectomy for hypersplenism, while all the others recovered successfully without surgical intervention. Of 9 cases of blunt splenic injury associated, however, with many potential postoperative complications (hemorrhage, subphrenic abscess, fistula, and pulmonary embolism) and with an increased long-term risk of severe bacterial infection, principally from Streptococcus pneumoniae, Neisseria meningitidis and Haemophilus influenzae, although vaccines now afford partial protection against these three. Thus recent reports have advocated nonoperative management of traumatic and spontaneous splenic rupture. Schuler et al. [8] described 17 patients (from 40 personal or published cases) so treated after spontaneous rupture of the spleen during infectious mononucleosis. Five required early-rescue splenectomy, and another a late splenectomy for hypersplenism, while all the others recovered successfully without surgical intervention. Of 9 cases of blunt splenic injury managed nonoperatively, according to the same criteria used for patients with injuries to normal spleens [11]. Some authors [12, 13] report success with nonoperative management in other infectious causes of spontaneous splenic rupture (such as malaria or dengue fever). Late complications appear to be rare and mainly involve splenic cysts and hypersplenism. The potential role of arteriographic embolization in this particular context has not been investigated.

We have demonstrated, as have others [5, 6], that nonoperative management can be safety and successfully used in patients with spontaneous splenic rupture secondary to primary CMV infection, when the patients are selected as recommended by Schuler et al. [8] and Rapp et al. [13], on the basis of initial hemodynamic stability without deterioration after volume replacement with crystalloids and blood. In conclusion, better knowledge of spontaneous splenic rupture due to primary CMV infection improves its management. Left upper abdominal pain with palpable splenomegaly in a young immunocompetent adult should be investigated by ultrasonography or CT scans or both to identify splenic rupture. Infectious mononucleosis is the most likely cause of spontaneous splenic rupture, but primary CMV infection should be systematically sought, although laboratory confirmation may be delayed. Because of the dramatic consequences of a missed diagnosis, infectious endocarditis and malaria should be ruled out by appropriate investigations. Splenectomy is required for initially unstable patients unresponsive to volume expansion, and nonoperative management should be chosen for those who are stable. The latter should be managed jointly with a surgical team, and the patient should be monitored in an intensive care unit. Antiviral agents are not recommended for primary CMV infection in immunocompetent individuals.

References