Cytomegalovirus Complicating Inflammatory Bowel Disease: Useful Remarks

Antonio Cascio, MD, PhD,1,2 Chiara Iaria, MD, PhD,1,3 Filippo Ricciardi, MD1 Giovanni Pellicani, MD1 Walter Fries, MD4

We read with great interest the paper by Al-Zaffri and colleagues on cytomegalovirus (CMV) infection in inflammatory bowel disease (IBD).1 We believe, however, that the potential occurrence of CMV pneumonia in the course of CMV infection in patients with IBD—as well as the possible role of CMV in triggering hemophagocytic lymphohistiocytosis (HLH) in that context—should also be considered.

HLH is a potentially fatal hyperinflammatory syndrome that is characterized by histiocytic proliferation and hemophagocytosis. The most typical presenting signs and symptoms are fever, hepatosplenomegaly, and cytopenia. Less frequently observed clinical findings are neurological symptoms, lymphadenopathy, edema, skin rash, and jaundice.2 Common laboratory findings include hypergammaglobulinemia, hypertriglyceridemia, hyperferritinemia, coagulopathy with elevated transaminase levels, and elevated tumor markers.3,3 HLH should be diagnosed using clinical criteria developed by the Study Group of the Histiocyte Society.4,5

The course of CMV infection in patients with IBD is worsening and/or associated with dyspnea.16 Treatment must be early and specific. In the presence of cytopenia (affecting ≥2 lines in the peripheral blood), a diagnosis of HLH should be suspected and may require combined antiviral and immunosuppressive treatment. The authors have no conflicts of interest to disclose.

References
6. Honbos C, Tiedemann C, Weckermann E et al. Definition of HLH can be established if 1 of the following is fulfilled:
   1. A molecular diagnosis consistent with HLH
   2. Diagnostic criteria for HLH (≥5 of the 8 criteria below)
   • Fever
   • Splenomegaly
   • Cytopenia (affecting ≥2 lines in the peripheral blood)
   • Hemoglobin <90 g/L (in infants <4 weeks: <70 g/L)
   • Fibrinogen ≤1.5 g/L
   • Ferritin ≥500 µg/L
   • Low or absent NK-cell activity
   • Hemophagocytosis in bone marrow, spleen, or lymph nodes
   • Splenomegaly
   • Fever
   • Low or absent NK-cell activity
   • Ferritin ≥500 µg/L
   • Neutrophils <1000/µL
   • Neutrophils ≤100/µL
   • < 1.5 µg/L

   Table. Hemophagocytic Lymphohistiocytosis (HLH) 2004 Diagnostic Criteria

   1. A molecular diagnosis consistent with HLH
   2. Diagnostic criteria for HLH
   3. Other abnormal clinical and laboratory findings consistent with HLH
   4. Other abnormal clinical and laboratory findings consistent with HLH
   5. Other abnormal clinical and laboratory findings consistent with HLH
   6. Other abnormal clinical and laboratory findings consistent with HLH
   7. Other abnormal clinical and laboratory findings consistent with HLH
   8. Other abnormal clinical and laboratory findings consistent with HLH

   Comments:
   • If hemophagocytic activity is not proven at the time of presentation, a further search for hemophagocytic activity is encouraged. If the bone marrow specimen is not conclusive, material may be obtained from other organs. Analysis of serial marrow aspirates over time also may be helpful.
   • The following findings may provide strong supportive evidence for the diagnosis of HLH: fever, cytopenia, splenomegaly, lymphadenopathy, and neurological symptoms. The histologic picture may resemble chronic persistent hepatitis (perihepatitis).
   • Other abnormal clinical and laboratory findings consistent with the diagnosis of hemophagocytic syndrome include fever, edema, jaundice, edema, skin rash, hepatic enzyme abnormalities, hypoproteinemia, hyperviscosity, increased VLDL, and/or decreased HDL.
   • HLH, high-density lipoprotein; NK, natural killer; VLDL, very-low-density lipoprotein.

   Figure 1. Cytomegalovirus pneumonia in patients with IBD was described: fever and dyspnea were the most frequently reported symptoms, and diffuse bilateral infiltrates were the main radiologic findings. Moreover, an initial chest radiograph failed to identify signs of pneumonia in 2 patients. Six cases were complicated by HLH. Eight patients were transferred to intensive care units, and 4 of them (1 with HLH) died. The two cases of CMV pneumonia occurred in patients with IBD in decompensation.

   Patients with IBD are at increased risk for CMV infection due to a new infection or reactivation. Generally, CMV infection should be suspected in patients with IBD who present with severe and/or refractory intestinal disease. However, CMV infection in patients with IBD can also lead to atypical pneumonia. CMV pneumonia should always be suspected in patients with IBD who present with fever and tachypnea, especially if the latter is worsening and/or associated with dyspnea. Treatment must be early and specific. In the presence of cytopenia (affecting ≥2 lines in the peripheral blood), a diagnosis of HLH should be suspected and may require combined antiviral and immunosuppressive treatment.

   We thank Cascio and colleagues1 for the interest expressed regarding our paper2 and for addressing cytomegalovirus (CMV) pneumonia and hemophagocytic lymphohistiocytosis (HLH) as other important complications of inflammatory bowel disease (IBD). Based on their review of the world literature between 1996 and 2011,3 they identified 13 cases that presented with a constellation of respiratory symptoms, including fever, tachypnea, and dyspnea. Twelve cases had abdominal chest radiographs. Four (31%) of the 13 patients with pulmonary involvement had CMV pneumonia. However, the incidence is unknown. Furthermore, this syndrome is relatively easy to diagnose. Cascio and colleagues1 suggest that this condition should have been considered in our report.

   The focus of our paper was the evaluation of gastrointestinal CMV as a complication of either ulcerative colitis or Crohn's disease. We were interested in the outcome of such patients with respect to IBD. We followed the definition of CMV disease outlined by Homberg and colleagues.4 Although the definitions overlap, in the review of Pillet and colleagues5 that was quoted by Cascio and colleagues,1 the definition of CMV disease is further refined into 3 levels: (1)
no intestinal involvement (including pneumonia), (2) intestinal involvement with systemic symptoms and endoscopic and virologic signs of CMV infection, and (3) local intestinal stigmata of CMV reactivation without signs of systemic or local disease. By this definition, our target was type 2 and, to some extent, type 3, which would not include other extraintestinal manifestations of CMV infections.

In light of the comments by Cascio and colleagues, we revisited the “control” population of patients with IBD who were reported to have been seen in the emergency room between January 2000 and November 2009 and looked for cases of CMV pneumonia. One man, age 62 years, with Crohn’s colitis complicated by bladder cancer with colonic metastases (without intestinal CMV involvement) was admitted to the intensive care unit with CMV pneumonia. He had a total 3-month hospitalization, but despite treatment with ganciclovir, he died in 2001 while in the hospital. We were unable to determine whether HLH was associated with the cause of death. As such, this patient was included in the 581-person control group because no intestinal disease with CMV was identified. This patient represents 0.17% of the control group.

In summary, we did not consider all CMV disease in our analysis but only intestinal involvement. In reviewing patients without intestinal involvement, we identified a single case of CMV pneumonia, supporting the notion that CMV pneumonia is a rare complication of IBD that is associated with increased mortality.

The authors have no conflicts of interest to disclose.

References