CORRESPONDENCE

Cytomegalovirus Complicating Inflammatory Bowel Disease: Useful Remarks

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We read with great interest the paper by Al-Zafiri 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—also should have been considered.

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

Two forms of the syndrome have been well characterized: familial HLH and sporadic HLH. The diagnosis of familial HLH requires either a positive family history of HLH or the presence of genetic mutations, such as aperforin gene mutations.[6] A number of triggers have been related to the development of HLH, including viral infectious agents (particularly Epstein-Barr virus and CMV), bacteria, parasites (eg, *Leishmania*), fungi, and medications such as immunosuppressors.[7-14] However, HLH may occur without any identifiable precipitating factor.

We have addressed these issues in a recently published systematic review of the literature.[15,16] In this review, the characteristics of 13 cases of CMV pneumonia in patients with IBD were 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.[15] Two cases of CMV pneumonia occurred in patients with IBD in deep remission.[17,18]

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 also can 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.[16] Treatment must be early and specific. In the presence of cytopenia (affecting ≥2 lineages in the peripheral blood), a diagnosis of HLH should be suspected and may require combined antiviral and immunosuppressive treatment.

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Table. Hemophagocytic Lymphohistiocytosis (HLH) 2004 Diagnostic Criteria[4,5]

The diagnosis of HLH can be established if 1 of the following is fulfilled: 1. A molecular diagnosis consistent with HLH 2. Diagnostic criteria for HLH (ie, 5 of the 8 criteria below) • Fever • Splenomegaly • Cytopenia (affecting ≥2 lineages in the peripheral blood) – Hemoglobin <90 g/L (in infants <4 weeks: hemoglobin <100 g/L) – Platelets <100,000/μL – Neutrophils <1000/μL • Hypertriglyceridemia and/or hypofibrinogenemia – Fasting trigycerides ≥265 mg/dL – Fibrinogen ≤1.5 g/L • Hemophagocytosis in bone marrow, spleen, or lymph nodes • Low or absent NK-cell activity • Ferritin ≥500 μg/L • Soluble CD25 ≥2400 U/L
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: spinal fluid pleocytosis (eg, presence of mononuclear cells) and/or elevated spinal fluid protein and/or a histologic picture that resembles chronic persistent hepatitis (per biopsy). • Other abnormal clinical and laboratory findings consistent with the diagnosis are cerebromeningeal symptoms, lymph node enlargement, jaundice, edema, skin rash, hepatic enzyme abnormalities, hypoproteinemia, hyponatremia, increased VLDL, and/or decreased HDL.

HDL, high-density lipoprotein; NK, natural killer; VLDL, very low-density lipoprotein.

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References

1. Al-Zafiri R, Gologan A, Galiatsatos P, Szilagyi A. Cytomegalovirus complicating inflammatory bowel disease: a 10-year experience in a community-based, university-affiliated hospital. *Gastroenterol Hepatol (N Y)*. 2012;8(4):230-239.
2. Aricò M, Janka G, Fischer A, et al. Hemophagocytic lymphohistiocytosis. Report of 122 children from the International Registry. FHL Study Group of the Histiocyte Society. *Leukemia*. 1996;10(2):197-203.
3. Janka GE. Familial hemophagocytic lymphohistiocytosis. *Eur J Pediatr*. 1983;140(3):221-230.
4. Gupta S, Weitzman S. Primary and secondary hemophagocytic lymphohistiocytosis: clinical features, pathogenesis and therapy. *Expert Rev Clin Immunol*. 2010;6(1):137-154.
5. Henter JI, Horne A, Aricò M, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer*. 2007;48(2):124-131.
6. Henter JI. Biology and treatment of familial hemophagocytic lymphohistiocytosis: importance of perforin in lymphocyte-mediated cytotoxicity and triggering of apoptosis. *Med Pediatr Oncol*. 2002;38(5):305-309.
7. Cascio A, Iaria M, Iaria C. Leishmaniasis and biologic therapies for rheumatologic diseases. *Semin Arthritis Rheum*. 2010;40(3):e3-e5.
8. Cascio A, Giordano S, Dones P, Venezia S, Iaria C, Ziino O. Haemophagocytic syndrome and rickettsial diseases. *J Med Microbiol*. 2011;60(pt 4):537-542.
9. Cascio A, Todaro G, Bonina L, Iaria C. Please, do not forget secondary hemophagocytic lymphohistiocytosis in HIV-infected patients. *Int J Infect Dis*. 2011;15(12):e885-e886.
10. David A, Iaria C, Giordano S, Iaria M, Cascio A. Secondary hemophagocytic lymphohistiocytosis: forget me not! *Transpl Infect Dis*. 2012;14(5):E121-E123.
11. Iaria C, Leonardi MS, Buda A, Toro ML, Cascio A. Measles and secondary hemophagocytic lymphohistiocytosis. *Emerg Infect Dis*. 2012;18(9):1529.
12. Pitini V, Cascio A, Arrigo C, Altavilla G. Visceral leishmaniasis after alemtuzumab in a patient with chronic lymphocytic leukaemia. *Br J Haematol*. 2012;156(1):1.
13. Cascio A, Pernice LM, Barberi G, et al. Secondary hemophagocytic lymphohistiocytosis in zoonoses. A systematic review. *Eur Rev Med Pharmacol Sci*. 2012; 16(10):1324-1337.
14. Atteritano M, Bagnato G, Beninati C, Iaria C, Cascio A. Secondary hemophagocytic lymphohistiocytosis in rheumatic diseases. A systematic review. *Eur Rev Med Pharmacol Sci*. 2012;16(10):1414-1424.
15. Cascio A, Iaria C, Ruggeri P, Fries W. Cytomegalovirus pneumonia in patients with inflammatory bowel disease: a systematic review. *Int J Infect Dis*. 2012;16(7):e474-e479.
16. Cascio A, Iaria C, Ricciardi F, Fries W. Comment to "Management of cytomegalovirus infection in inflammatory bowel diseases." *Dig Liver Dis*. 2013;45(2):176.
17. Lo Presti MA, Costantino G, Della Torre A, Belvedere A, Cascio A, Fries W. Severe CMV-related pneumonia complicated by the hemophagocytic lymphohistiocytic (HLH) syndrome in quiescent Crohn's colitis: harmful cure? *Inflamm Bowel Dis*. 2011;17(11):E145-E146.
18. Hookey LC, Depew W, Boag A, Vanner S. 6-mercaptopurine and inflammatory bowel disease: hidden ground for the cytomegalovirus. *Can J Gastroenterol*. 2003;17(5):319-322.

Response

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We thank Cascio and colleagues[1] for the interest expressed regarding our paper[2] 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 abnormal chest radiographs. Four (31%) of the 13 patients died. Given the paucity of cases reported, CMV pneumonia must be quite rare, although the exact incidence is unknown. Furthermore, this syndrome is relatively easy to diagnose. Cascio and colleagues[1] 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 Hommes and colleagues.[4] Although the definitions overlap, in the review of Pillet and colleagues[5] that was quoted by Cascio and colleagues,[1] the definition of CMV disease is further refined into 3 levels: (1)

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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,[1] 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

1. Cascio A, Iaria C, Ricciardi F, Pellicanò G, Fries W. Cytomegalovirus complicating inflammatory bowel disease: useful remarks. *Gastroenterol Hepatol (N Y)*. 2013;9(11):756-757.
2. Al-Zafiri R, Gologan A, Galiatsatos P, Szilagyi A. Cytomegalovirus complicating inflammatory bowel disease: a 10-year experience in a community-based, university-affiliated hospital. *Gastroenterol Hepatol (N Y)*. 2012;8(4):230-239.
3. Cascio A, Iaria C, Ruggeri P, Fries W. Cytomegalovirus pneumonia in patients with inflammatory bowel disease: a systematic review. *Int J Infect Dis*. 2012;16(7):e474-e479.
4. Hommes DW, Sterringa G, van Deventer SJ, Tytgat GN, Weel J. The pathogenicity of cytomegalovirus in inflammatory bowel disease: a systematic review and evidence-based recommendations for future research. *Inflamm Bowel Dis*. 2004;10(3):245-250.
5. Pillet S, Pozzetto B, Jarlot C, Paul S, Roblin X. Management of cytomegalovirus infection in inflammatory bowel diseases. *Dig Liver Dis*. 2012;44(7):541-548.