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Cytomegalovirus Associated Hemophagocytic Lymphohistiocytosis in Patients Suffering from Crohn's Disease Treated by Azathioprine: A Series of Four Cases

To the Editor:

We report here a series of human cytomegalovirus (HCMV)-related hemophagocytic lymphohistiocytosis (HLH) cases (HCMV-HLH) that occurred during the 2009–2010 period in four female patients age 32.2 ± 3.7 years suffering from Crohn's disease (CD). Azathioprine was the current treatment for all of them, whereas two had received antitumor necrosis factor (TNF) (Table 1).

Fever, cytopenia, hyperferritinemia, and hypertriglyceridemia were present in all cases. Bone marrow aspiration showed macrophagic hyperplasia and erythrophagocytosis in each case and the diagnosis of HLH was established using the referenced clinical and biological parameters as described in Table 1.¹ A mild 2N transaminases elevation with hyperbasophilic mononuclear cells on complete blood count was present in all of these cases. HCMV plasma viral load and IgG and IgM serologies were positive for each patient, with a low IgG avidity index supporting a HCMV primo-infection (Table 1). Moreover, no other relevant infectious (*Mycobacterium tuberculosis*, *Mycoplasma pneumoniae*, *Epstein*

Barr virus, *Herpes simplex*, etc.) or noninfectious etiological causes (lymphoma, etc.)² were seen in the study patients (not shown).

All four patients received corticoids and an antiviral therapy (ganciclovir and/or valganciclovir), whereas azathioprine and anti-TNF were withdrawn at the time of hospitalization (Table 1). The clinical course was good for two patients (Cases 1 and 2) with apyrexia, cytopenia resolution, and an undetectable HCMV peripheral blood plasma viral load (<500 genome copies/mL) 15 days later. For Cases 1 and 2, corticotherapy and antiviral therapy were discontinued at 6 and 4 months, respectively. Moreover, these patients received an anti-TNF in association with antiviral therapy that was introduced or reintroduced without HCMV-HLH relapse at 2 and 3 months, respectively. For these two patients, the clinical outcome was good 21 and 15 months later.

A pericarditis with tamponade and an acute colitis due to CD and HCMV infection was diagnosed in Case 3 and a bilateral HCMV pneumoniae was evident in Case 4 (HCMV bronchoalveolar lavage viral load 19 200 copies/mL without any other relevant pathogen seen by classical and molecular microbiological techniques). These two patients required intensive care unit admission. An absence of favorable hematologic response with corticosteroids required the introduction of polyvalent immunoglobulins and foscarnet antiviral therapies in both Cases 3 and 4. Total colectomy was performed in Case 3, whereas an emergency surgery related to the perforation of two necrotic gastric ulcers was necessary in Case 4. The clinical outcome was good 9 months later for Patient 3, whereas Patient 4 died during emergency surgery.

We report the largest monocentric series of CD patients experiencing HCMV-HLH. All of our patients were female, which might be due to the sex

ratio of 1.3 female to 1 male for CD patients in northern France.³ The occurrence of these four study cases over a short period could be explained by the fact that all CD patients treated by azathioprine hospitalized for unexplained fever and cytopenia were not systematically considered for azathioprine toxicity and therefore were also screened for HLH by ferritinemia, triglyceridemia, and then in cases of abnormal values by a bone marrow aspiration. This approach was systematically conducted in order to obtain a sufficient number of diagnostic criteria.¹ In cases of histological confirmation of HLH, real-time polymerase chain reaction (PCR) techniques for the detection of an ongoing human *herpesviridae* infection were performed.⁴ HCMV is recognized to be one of the main infectious causes of HLH in adult CD patients^{4–6} with *Epstein Barr virus*⁷ and *Mycobacterium tuberculosis*.⁵ Because all of the patients experienced azathioprine during the years before, and that only two of them had been previously treated by anti-TNF for a shorter period, we suspected a potential role of azathioprine treatment in the genesis of HCMV-HLH. Moreover, anti-TNF treatment was reintroduced in Patients 1 and 2 without HCMV-HLH relapse, supporting the hypothesis of a nondeleterious role of anti-TNF in the course of the HCMV-related HLH in these patients. Further larger prospective and multicentric studies would be necessary to investigate the potential deleterious role of azathioprine compared to that of anti-TNF treatment in the development of HCMV-HLH in patients with CD. In the present report, neither azathioprine treatment length nor HCMV plasma viral load levels appeared to be potentially related to a worse prognosis in HCMV-HLH (Table 1). Moreover, the prognosis of focal organ damage such as pericarditis, colitis, or pneumonia and the clinical significance of persistent high ferritinemia values during the course of the HLH⁸ remain to be

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TABLE 1. Demographic Clinical and Biological Characteristics of the Four Study HCMV-HLH Patients

	Case 1	Case 2	Case 3	Case 4
Sex (M/F)	F	F	F	F
Age (years)	28	33	30	38
Treatment received for Crohn's disease:				
Azathioprine (length of treatment in years)	+ (5)	+ (5)	+ (4)	+ (2)
Anti-TNF (length of treatment in years)	+ (2)	—	+ (0.08)	—
Fever	+	+	+	+
Lymphadenopathy	—	+	—	—
Hepatosplenomegaly	—	—	—	—
Pericarditis	—	—	+	—
Colitis	—	—	+	—
Pneumopathy	—	—	—	+
Cytopenia	+	+	+	+
Hyperbasophilic mononuclear cells (% on CBC)	+ (8)	+ (8)	+ (2)	+ (9)
Ferritinemia on admission (>500 ng/mL) (N < 190 ng/mL)	2380	2100	4020	22400
Maximal ferritinemia during hospitalization (N < 190 ng/mL)	2380	2100	4170	52900
Triglyceridemia (>3.0 mmol/L) (N < 1.71)	3.16	3.49	2.32	5.07
Bone marrow aspiration				
Macrophagic hyperplasia	+	+	+	+
Erythrophagocytosis	+	+	+	+
HCMV IgG serology	+	+	+	+
HCMV IgM serology	+	+	+	+
HCMV IgG avidity index <i>CLIA Diasorin</i> *	0.19	0.05	0.18	0.03
HCMV plasma viral load (copies/mL)	173 000	390 000	74 600	154 000
Delay between treatment and onset of disease (days)	7	29	38	15
Therapeutic management				
Corticotherapy	+	+	+	+
Polyvalent Immunoglobulins	—	—	+	+
Ganciclovir/valganciclovir	+	+	+	+
Foscarnet	—	—	+	+
Azathioprine withdrawal	+	+	+	+
Anti-TNF withdrawal	+	NA†	+	NA
Outcome	Survived	Survived	Survived	Dead
Anti-TNF introduction without HCMV-HLH relapse	+	+	—	NA

CBC, complete blood count. NA, not applicable.

*CLIA Diasorin, liaison index <0.2 when infection occurred within the past 3 months.

Bold = Criteria definition for the diagnosis of hemophagocytic syndrome¹: diagnosis is confirmed when five criteria are fulfilled and highly possible when four criteria are fulfilled.

fully investigated in further prospective larger studies.

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REFERENCES

1. Fardet L, Lambotte O, Meynard JL, et al. Reactive haemophagocytic syndrome in 58 HIV-1-infected patients: clinical features, underlying diseases and prognosis. *AIDS*. 2010;24:1299–1306.
2. Créput C, Gallicier L, Buyse E, et al. Understanding organ dysfunction in hemophagocytic lymphohistiocytosis. *Intensive Care Med*. 2008;34:1177–1187.
3. Gower-Rousseau C, Salomez JL, Dupas JL, et al. Incidence of inflammatory bowel

- disease in northern France (1988–1990). *Gut*. 1994;35:1433–1438.
4. Kohara MM, Blum RN. Cytomegalovirus ileitis and hemophagocytic syndrome associated with use of anti-tumor necrosis factor- α antibody. *Clin Infect Dis*. 2006;42:733–734.
 5. James DG, Stone CD, Wang HL, et al. Reactive hemophagocytic syndrome complicating the treatment of inflammatory bowel disease. *Inflamm Bowel Dis*. 2006;12:573–580.
 6. Miquel T, Bonnet DP, Leport J, et al. Hemophagocytic syndrome in the course of Crohn's disease: possible association with cytomegalovirus infection. *Am J Gastroenterol*. 2009;104:252.
 7. Francolla KA, Altman A, Sylvester FA. Hemophagocytic syndrome in an adolescent with Crohn disease receiving azathioprine and infliximab. *J Pediatr Gastroenterol Nutr*. 2008;47:193–195.
 8. Esumi N, Ikushima S, Todo S, et al. Hyperferritinemia in malignant histiocytosis and virus associated hemophagocytic syndrome. *N Engl J Med*. 1986;316:346–347.