only.[1–3] We describe here the first documented Influenza virus (subtype H3N2) infection in a patient with complete IFN-γR1 deficiency.

A 4-year old boy with AR IFN-γR1 (c.523delT/c.652_654delGAA) managed with long-term triple antibiotics (azithromycin, ciprofloxacin and cotrimoxazole) because of a previous disseminated *M. fortuitum* infection, presented with low-grade fever (38.2°C), cough, nausea and vomits, while awaiting matched sibling donor hematopoietic stem cell transplantation (HSCT). Forty-eight hours earlier, his mother showed mild upper respiratory symptoms. Nasopharyngeal swabs taken from the mother and patient were positive for influenza A virus using a rapid antigen test *(BD Directigen™, EZ Flu A+B*). Polymerase chain reaction testing (*Simplexa Flu A/B & RSV Direct*) confirmed the diagnosis of influenza H3N2 subtype. Neither the patient nor the family members including the matched sibling donor had received seasonal influenza vaccination. Treatment with oseltamavir (30 mg/12 h/vo during 5 days) for the patient and prophylaxis for the donor (30 mg/24 h/vo during 5 days) was initiated; the patient became afebril within 24 hours while upper respiratory symptoms persisted for another 7 days. Repeated polymerase chain reaction testing for influenza H3N2 remained positive for 10 days after stopping antiviral treatment. During this episode, serum IFN-γ values were raised (>200 pg/ml, normal <40), and HSCT was delayed for 6 weeks with normalizing IFN-γ levels. Subsequently, a fully myeloablative, non-T lymphocyte-depleted matched sibling donor transplant was performed without mayor complications, and currently, 17 months after HSCT, he remains in excellent clinical condition with no signs of graft versus host disease and a stable donor chimerism of >95% without any specific treatment.[3]

This is the first documented case of a patient with AR IFN-γR1 deficiency suffering from influenza A virus infection as well as pre HSCT. Despite antibiotic treatment, complete IFN-γR1 deficiency is fatal in almost all cases within the first 20 years of life. HSCT remains the only curative treatment.[1] Although data are promising for influenza vaccine effectiveness in patients with complete interleukin-12/23 receptor-β1 and partial IFN-γ R1 deficiencies, information is lacking for patients with complete IFN-γ R1 deficiencies.[4] Although our patient showed only mild clinical symptoms and recovered under ambulant antiviral therapy, systematic influenza vaccination and subsequent determination of vaccine responses in affected patients, their families and potential HSCT donors should be considered in these patients as recently proposed by the Infectious Diseases Society of America, thereby preventing potentially severe complications or HSCT delay.[5,6]

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Hemophagocytic Lymphohistiocytosis in Children With Visceral Leishmaniasis

To the Editor:

In the July 2015 issue of *The Pediatric of Infectious Disease Journal*, Blázquez-Gamero et al[1] reported a study analyzing the relationship between visceral leishmaniasis (VL) in children and acquired hemophagocytic lymphohistiocytosis (HLH) syndrome. Twenty-four children with VL were studied and 10 (41%) developed HLH syndrome. In HLH, there is a disorder of the activation and proliferation of T-cells and macrophages, with subsequent cytokine production, leading to uncontrolled inflammation. Acquired HLH is associated with several infections, particularly Epstein-Barr virus and other herpesvirus infections, and less frequently with *Leishmania* infections.[1,2]

We conducted a retrospective study of VL in children who were cared for in 3 hospitals in the Alicante province of Spain, on the Mediterranean coast, from July 1993 to June 2015. The diagnostic criteria for HLH are those proposed in 2004 by the Hemophagocytic Lymphohistiocytosis Study Group.[3] Soluble interleukin-2 receptor (sCD25) in plasma and natural killer cell activity were not measured. Quantitative variables were analyzed by Student *t* test and qualitative variables by the Fisher exact test.

Thirty-eight children were diagnosed with VL during the study period. Twenty-five children were studied. Data for the presence of fever or splenomegaly and complete blood count and serum triglyceride were recorded during 96 hours after diagnosis. Eight children (32%; 95% confidence interval: 17.2%–51.9%) met criteria for HLH syndrome. Table 1 shows HLH criteria and other clinical and epidemiologic characteristics of the patients analyzed. Patients with HLH had significantly lower hemoglobin ($P = 0.004$) and platelets ($P = 0.01$) and higher ferritin ($P = 0.001$) and serum triglycerides ($P = 0.005$). Bone marrow aspirates were performed in 17 children, and none had findings of hemophagocytosis. No specific

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TABLE 1. Differences of Children With and Without HLH Syndrome

	Children With HLH (n = 8)	Children Without HLH (n = 17)	*P* Value	Missing Values
Age, median (SD)	31.5 (28.5)	36.6 (30.1)	0.167	0
Sex, male, n (%)	5 (62.5)	7 (41.2)	0.411	0
Fever, n (%)	8 (100)	16 (94.1)	1	0
Days of fever, median (SD)	11.6 (5.7)	20.5 (14.9)	0.129	4
Hepatomegaly, n (%)	5 (62.5)	14 (82.4)	0.344	0
Splenomegaly, n (%)	8 (100)	17 (100)	1	0
Hemoglobin (g/L), median (SD)	6.7 (0.7)	8.1 (1.2)	0.004	0
Platelets ($\times 10^3/\mu L$), median (SD)	50.7 (33.5)	92.1 (37.8)	0.015	0
Neutrophils ($\times 10^3/\mu L$), median (SD)	689 (319)	843 (502)	0.437	0
Aspartate aminotransferase (U/L), median (SD)	91 (66)	216 (350)	0.332	0
Alanine aminotransferase (U/L), median (SD)	48 (37)	135 (160)	0.152	0
Erythrocyte sedimentation rate, median (SD)	61 (7)	75 (27)	0.331	8
Triglycerides (/mL), median (SD)	521 (284)	236 (85.8)	0.001	0
Fibrinogen (mg/mL), median (SD)	234 (135)	333 (150)	0.343	16
Ferritin (ng/mL), median (SD)	2177 (820)	800 (1129)	0.005	0
Immunoglobulin G (mg/mL), median (SD)	1622 (633)	2067 (1076)	0.666	12
Treatment with liposomal amphotericin B, n (%)	7 (87.5)	12 (70.6)	0.624	0
Outcome, cure, n (%)	8 (100)	17 (100)	1	0

SD indicates standard deviation.

treatment for HLH was given. All of our patients, whether or not they had HLH, had favorable outcomes with either liposomal amphotericin B or sodium stibogluconate treatment.

In the study of Bode et al,[2] VL-associated HLH represented 2.1% (15 of 710) of all HLH cases included in a national reference center database. In the study by Blázquez-Gamero et al,[1] 41% of children met HLH criteria. In our study, the percentage of VL-associated HLH in children was lower than that reported in the study by Blázquez-Gamero et al[3] and higher than that reported in the study by Bode et al.[2]

HLH has a varied presentation with nonspecific signs and symptoms. In secondary forms of HLH, remission may be achieved by treating the underlying disease. Recently, tocilizumab, a humanized monoclonal antibody against the interleukin-6 receptor, has been shown to regulate the immune response for VL with HLH.[4] In our study, favorable outcome was achieved only by treating the underlying VL.

Although we did not find any signs of hemophagocytosis in our bone marrow samples, Hussein et al[5] stress importance of a careful examination of bone marrow for this. In our retrospective study, we found results similar to those who demonstrated that secondary HLH can occur with VL as part of the natural history of this disease and that it does not imply a worse prognosis if the infection is treated properly.

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