Disseminated cytomegalovirus-associated hemophagocytic lymphohistiocytosis in an elderly patient

TO THE EDITOR: Hemophagocytic lymphohistiocytosis (HLH) is characterized by severe immune activation and deregulation resulting in extreme and often life-threatening inflammation [1]. Adult-onset HLH is rare and fatal. Infectious agents contribute to a major part of the etiology of adult-onset HLH [2, 3]. A high degree of clinical suspicion and prompt treatment is required to prevent mortality. We have described an unusual clinical presentation of a case of cytomegalovirus (CMV)-associated HLH with multi-organ involvement.

CASE

A 71-year-old man presented with altered mental status, fever, and multi-organ dysfunction. His symptoms began 2 months ago with gradually progressive fatigue, generalized maculopapular rash, arthralgias, fever, anemia, pneumonia, and acute renal insufficiency at a hospital admitted previously. Preliminary laboratory tests for infection and autoimmune diseases were all negative. The rash and arthralgia developed after a recent travel to India (how long did he stay there?). The physical examination was unremarkable except for left hemiparesis and right-sided Bell's palsy. The initial laboratory results were as follows: hemoglobin, 94 g/L; white blood cell (WBC) count, 15.1×10^9/L; platelets, 42×10^9/L; and neutrophils, 90%. The results of his cerebrospinal fluid (CSF) studies were suggestive of meningitis with high protein level, low glucose level, and increased number of lymphocytoid cells. Bronchoalveolar lavage (BAL) fluid culture revealed growth of *Klebsiella pneumoniae*. After admission, the patient was treated with broad-spectrum antibiotics, steroids, and anti-tuberculosis therapy. Over the next few days, his condition worsened due to anemia, pancytopenia, and abnormal renal and liver functions. His ferritin level was progressively increasing, with a peak level of >3,000 ng/mL. Brain magnetic resonance imaging (MRI) studies revealed sulci expansion and abnormal signals over the subarachnoid spaces. The patient did not have any evidence suggestive of an immunocompromised state.

Considering the progressive pancytopenia, multiorgan dysfunction, low fibrinogen level, and high ferritin level, a provisional diagnosis of HLH was made. His serum soluble IL-2R level elevated to 1,054 pg/mL. Peripheral blood smear revealed normocytic hypochromic anemia with moderate anisopoikilocytosis. Numerous histiocytes with evidence of hemophagocytosis were observed in bone marrow aspiraion without any significant dysplasia (Fig. 1A, B). Granuloma or fibrosis was not observed. Fungal and acid-fast staining were negative. Meanwhile, owing to the worsening pneumonia, the patient underwent follow-up BAL and showed cytomegalovirus (CMV)-positive by polymerase chain reaction (PCR). At the same time, peripheral blood PCR showed 154,111 copies/mL of CMV, and a repeat CSF analysis also showed CMV-positive by PCR. Immunohistochemical staining in the BM biopsy was positive for CMV (Fig. 1C). Overall, the findings were compatible with a diagnosis of disseminated CMV-associated HLH. The patient was admitted to the intensive care unit. However, in spite of all the measures taken, including immunosuppressive treatment with etoposide, and broad-spectrum antibiotics and ganciclovir for CMV, he died 2 weeks after the confirmation of the diagnosis of CMV-associated HLH.

DISCUSSION

HLH occurs as either a primary (familial) [4] or a secondary (sporadic) disorder [5, 6]. Both conditions manifest pathological immune activation and may be difficult to differentiate from each other. Primary HLH is an autosomal recessive disease with an incidence of 1 per 50,000 live-born children [5]. Younger patients often have a clear familial

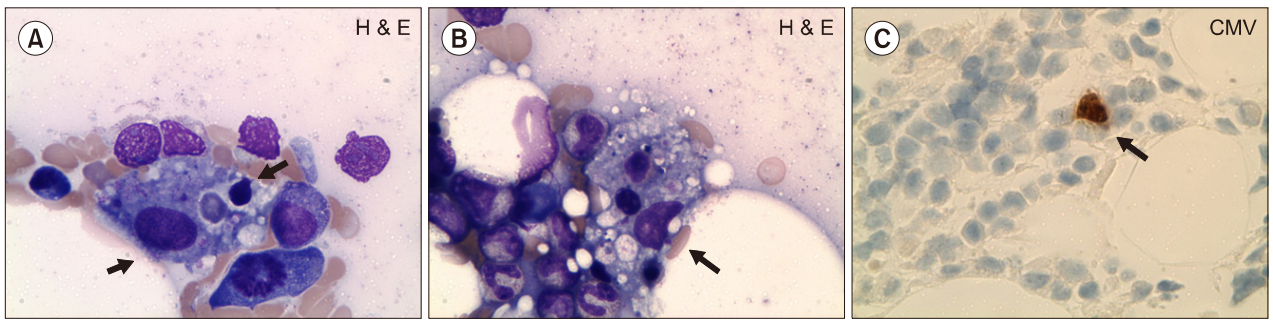

Fig. 1. **(A–C)** Features of the bone marrow (BM) aspirate and biopsy showing hemophagocytic lymphohistiocytosis (HLH) and cytomegalovirus (CMV) staining. **(A, B)** BM aspirate showing histiocytic hyperplasia and prominent hemophagocytosis by activated histiocytes. Arrowheads indicate features suggestive of ongoing endocytosis (Wright-Giemsa stain, ×1,000). **(C)** BM core biopsy result showing positive immunohistochemical stain for CMV showing a large cell with intranuclear inclusions suggestive of CMV in the BM.

inheritance or genetic mutation. The median survival is <2 months if untreated. Immunological triggers such as vaccinations and viral infections may trigger bouts of disease in these patients. However, in many circumstances, no clear-cut immunological trigger is identifiable. Secondary HLH [7] includes adults and older children who lack a family history or known genetic cause of HLH. The diagnostic criteria for HLH were mainly derived from studies in the pediatric population, but characteristics of adult HLH are now recognized [8]. Secondary HLH often occurs as a result of pathological immune activation in response to a trigger. The frequently noted triggers include malignancy [9] (especially hematological malignancies, including acute leukemia, myelodysplastic syndrome, and myelofibrosis), infections (especially viruses such as EBV and CMV), and rheumatological disorders [2, 8, 10]. Immune-activated and immune-mediated pathologies likely play a central role in the evolution of HLH. These represent acute clinical signs and symptoms of immune activation, including hepatomegaly, jaundice, adenopathy, rash, seizures, and focal neurologicneurological deficits, as well as abnormaly high serum level of cytokines such as interferon gamma (IFN γ), tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), IL-10, and macrophage-colony stimulating factor (M-CSF) [11, 12]. Biopsies of lymphoid tissues or histological examination of liver tissue from HLH patients reveals highly activated macrophages and lymphocytes, supporting striking activation of the immune system [10]. Therefore, the goal of initial therapy is to suppress the hyperactive immune system for preventing immune-mediated irreversible organ damage [13]. Induction therapy is often followed by allogeneic stem cell transplantation if a suitable donor is available. If no suitable donor is identified, patients should be followed up closely for signs of relapse. The HLH-94 protocol proposed in 1997 [14] included an 8-week regimen of etoposide, dexamethasone, and intrathecal methotrexate. The clinical profile of our patient was complex, and HLH in an elderly patient without any preexisting factor supporting an immunocompromised state is unusual. The clinical features that raised the suspicion of HLH were fever, cytopenia, organomegaly, coagulopathy, liver function abnormalities, elevated ferritin level, and hemophagocytic lymphohistiocytic in the BM. Disseminated CMV associated with HLH is uncommon in adults, and anecdotal pediatric cases were reported [15]. Early recognition and treatment of HLH are essential, and rare pathogens such as CMV should be considered as a cause of HLH.

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Steps taken to alleviate under-reporting of transfusion reactions at a public sector hospital in Pakistan

TO THE EDITOR: A transfusion reaction (TR) is any untoward event that occurs during or after blood transfusion and is not related to the patient's underlying illness. It has been estimated that about 10% of all transfusions carry the risk of an adverse event [1]. Both, infectious and non-infectious TRs are associated with significant mortality and morbidity [2]. The frequency of TR is estimated to be 0.5 to 2.9 per 1,000 blood units [3-6]. However, the actual TR incidence is frequently underestimated; therefore, every hospital should have a hemovigilance program aimed at effectively reporting and analyzing TR in order to improve transfusion patient safety [5].

Here we describe a clinical audit conducted at the Isratul Ebad Khan Institute of Blood Diseases (IEKIBD), Dow University Hospital, Pakistan. The audit was undertaken as an institutional effort towards hemovigilance with the aim of observing the frequency of reported TRs and assessing the effects of measures taken to avoid TR under-reporting. A standard TR investigation protocol was used (Fig. 1) and TRs were classified according to standard AABB definitions.

From January to December 2013, approximately 3,960 blood units were released for transfusion. Out of these blood units, only one febrile non-hemolytic transfusion reaction (FNHTR) was reported. The estimated rate of TR was found to be 0.2 per 1,000 blood units administered (Table 1). This rate of TR was found to be low when compared to local and international studies, where the rate of TRs per 1,000 units was 0.93 to 1.16 [3, 4] and 0.4 to 2.9 [5, 6], respectively. To investigate the root cause of this presumed under-reporting of TR, we designed and distributed an in-house questionnaire regarding the signs and symptoms of TRs to evaluate the ability of medical and nursing staff to recognize and report any adverse TR. An open-ended question was included about the reasons for not reporting a TR. On evaluation, it was found that about 73% of medical and nursing staff were well aware of the signs and symptoms of TR. Reasons for TR under-reporting were found to be multifactorial and mainly included a lack of easy accessibility of TR forms in different hospital units, a lack of awareness about existing TR reporting systems among newly inducted interns and residents, and the irrational use of transfusion premedication (antihistamines and NSAIDs) without knowing the patient's previous history of TR.

The following steps were then taken to improve overall TR reporting:

1. Easy accessibility of TR forms: To improve the accessibility of TR forms, we printed them on the reverse side of the cross-match product releasing slip, so that every unit of blood leaving the blood bank would automatically be accompanied by a TR form.

2. TR Awareness sessions: Interactive sessions with nursing/medical staff were carried out to familiarize them with the institution's existing system for reporting TR. Information flyers were also distributed highlighting the cardinal signs and symptoms of TR to enhance staff's ability to identify TRs.

3. Discouraging transfusion pre-medication: Based on the results of a literature search [7], the use of transfusion premedication was discouraged in patients receiving a transfusion for the first time as it could mask the likely occurrence of FNHTR or allergic transfusion reaction (ATR), as well as giving the potential to miss a more severe reaction like acute hemolytic transfusion reaction (HTR) or a septic reaction.

A post-audit analysis was conducted from January to December 2014. Overall, 5,940 blood products were transfused and 20 TRs were reported. The rate of reported TRs was 3.4 per 1,000 blood products administered. Of the 20 TRs, 16 occurred in women and 4 in men. The median patient age was 40 years (±20 years). The frequency of TR was highest for PRBC (4.5/1,000) transfusion, followed by platelets (2.2/1,000), and fresh frozen plasma (0.3/1,000). The spectrum of adverse TRs noted with different blood products is shown in Table 1. ATR was the most frequent adverse event, accounting for 60% of all events, followed by FNHTR, which accounted for 40%. Medical and nursing staff equally reported these reactions. No transfusion reaction occurred because of clerical errors, including ABO-mismatched component transfusion. Following the implementation of new strategies, the rate of TR was increased from 0.2 to 3.4 per 1,000 transfusions.

In this study, the result of the initial audit was consistent with the assumption of under-reporting of TR. The post-audit rate of TR in our study was the same as the ones in the studies from countries like the Netherlands and Namibia, which were 3.3 and 3.4 per 1,000 units, respectively [8, 9]. However, it was higher than the results of previous studies from Pakistan, which were 0.8 and 1.16 per 1,000 units [3, 4]. Most of the authors of previous studies identified an inability to recognize TRs as the most common reason for the under-reporting of the events [10]. However, in this study we found that irrational use of transfusion premedication, unavailability of TR forms, and limited information on the institutional TR reporting system among health care workers were common reasons for TR under-reporting. The efficacy of pre-transfusion medication for the prevention of acute TRs like FNHTR and ATR have