A Case of Human Immunodeficiency Virus -triggered Hemophagocytic Lymphohistocytosis Presenting with Severe Bleeding Tendency

Bongyoung Kim, Yeon Woo Choi, Hyunjoo Pai, and Jieun Kim

Department of Internal Medicine, Hanyang University College of Medicine, Seoul, Korea

ABSTRACT

Human immunodeficiency virus (HIV) is one of the less common triggers of secondary hemophagocytic lymphohistocytosis (HLH) in which coagulation disorder is a frequent manifestation. Here, we present a case of HIV-triggered secondary HLH presenting with severe bleeding tendency and fever. Despite high-dose dexamethasone infusion (10 mg/body surface area/day), progressive disseminated intravascular coagulation and thrombocytopenia resulted in massive hemathochezia: the bleeding episode ceased after endoscopic hemoclipping. After then, he took a highly-active antiretroviral therapy (HAART). Eventually, body temperature and overall laboratory findings normalized in response to HAART. Clinicians should not overlook HIV infection as a possible trigger of secondary HLH. In such cases, HAART is the core treatment.

Keywords: Human immunodeficiency virus; Acquired immune deficiency syndrome; Antiviral

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare disease caused by an unusually strong immune response and unregulated activated macrophages and overproduction of inflammatory cytokines frequently result in life-threatening conditions [1]. It typically has a rapidly-progressing course and is often confused with sepsis because the two have similar clinical manifestations and laboratory findings [1]. Coagulation disorders due to disseminated intravascular coagulation (DIC) and thrombocytopenia are also common in HLH patients and are associated with adverse outcome [2].

Secondary HLH can be provoked by infections, malignancies, and autoimmune diseases [1]. A French study found that hematological malignancies (in particular non-Hodgkin lymphomas) were the main trigger of HLH, accounting for 56.8% of cases and infections were considered as trigger in 24.7% of cases [3]. In the same study, 6.1% of 162 HLH patients were provoked by virus [3]. In comparison, a Japanese study described Epstein-Barr virus (EBV) was the most common trigger, followed by other infections or lymphomas [4]. Indeed, various viral agents such as EBV, cytomegalovirus, parvovirus B19, etc. play a role in the origin of secondary HLH [3-5]. Human immunodeficiency virus (HIV) is also a less common trigger [5].
The overall mortality rate of HLH exceeds 50% [3]. In particular, HLH patients with hematological malignancies have a marked poorer outcome compared with those with infections or autoimmune diseases [5]. When triggers are adequately controlled, the better outcomes could be achieved [3]. Here, we present a case of HIV-triggered secondary HLH that presented with severe bleeding tendency and was successfully treated by highly-active antiretroviral therapy (HAART).

CASE REPORT

A 25-year-old man was referred to a university-affiliated hospital with one week-long fever, myalgia, and sore throat. He had no medical history except for childhood appendectomy. On admission his vital signs were: blood pressure 130/65 mmHg, body temperature 37.4°C, pulse 78 beats/min, respiratory rate 18 breaths/min, with awake and alert. On physical examination, multiple lymph node enlargement was observed. Initial complete blood count and blood chemistry were: leukocytes 5,600/mm³ (segmented neutrophil 41%, lymphocyte 43.7%), hemoglobin 14.0 g/dL, platelets 159,000/mm³, blood urea nitrogen 14.4 mg/dL, creatinine 0.79 mg/dL, aspartate transaminase 748 U/L, alanine transaminase 609 U/L, alkaline phosphatase 52 U/L, total bilirubin 0.42 mg/dL, lactate dehydrogenase 1,654 U/L, creatine phosphokinase 112 U/L, c-reactive protein 1.75 mg/dL, ferritin 51,059 ng/mL, and triglyceride 136 mg/dL. On abdominal computed tomography examination, hepatosplenomegaly and enlargement of multiple intra-abdominal lymph nodes were observed (Fig. 1). In additional laboratory tests to differentiate other infectious diseases, the results were as follows: serum cytomegalovirus polymerase chain reaction (PCR) negative, EBV IgM negative, Hepatitis A virus (HAV) IgM negative, HBSAg negative, HBeAb IgM negative, Hepatitis C virus (HCV) antibody negative, S. typhi O <1:20, S. typhi H 1:20, blood culture negative, and HIV enzyme-linked immunosorbent assay positive. Based on these findings we suspected acute HIV syndrome, maintained conservative treatment and waited for the result of western blot tests.

On hospital day 4, ecchymoses developed on the dorsa of both feet where peripheral venous catheters were inserted and his body temperature was still above 38.5°C. In addition, thrombocytopenia, hyperferritinemia, and DIC were observed in follow-up laboratory tests: platelets 75,000/mm³, ferritin 181,875 ng/mL, fibrinogen 106 mg/dL, d-dimer 34.28 mg/L,

Figure 1. Abdominal computed tomography findings (on hospital day 1). (A) hepatosplenomegaly (B) enlargement of multiple intra-abdominal lymph nodes (white arrows)
prothrombin time 1.52 (international normalized ratio), and fibrin degradation product 207.4 μg/mL. To identify the cause of the hematologic abnormality we performed a bone marrow biopsy the following day. The findings were compatible with HLH: Wright-Giemsa staining revealed six percent histiocytes, which phagocytize erythrocytes, along with segmented neutrophils and platelets (Fig. 2). Intravenous high-dose dexamethasone (10mg/body surface area/day) infusion was started, but the patient complained of massive hemathochezia, and hemoglobin declined from 10.6 g/dL to 6.8 g/dL on hospital day 6. Upper endoscopy was immediately performed and showed arterial bleeding with an ulcerative lesion on the duodenal bulb (Fig. 3). After endoscopic hemoclipping, the bleeding episode ceased, and the patient’s general condition improved gradually, although high fever and thrombocytopenia persisted.

Figure 2. Histopathologic features of the bone marrow of the 25-year-old man with HLH associated with acute human immunodeficiency virus (HIV) syndrome (Wright-Giemsa stain, x400): microscopic examination revealed the presence of six percent histiocytes, which phagocytize erythrocytes (red arrows), along with segmented neutrophils and platelets.

Figure 3. Upper endoscopy findings (on hospital day 6): submucosal arterial bleeding with ulcerative lesions on the duodenal bulb.
The results of HIV tests were reported on hospital day 11: the western blot assay was positive and HIV ribonucleic acid PCR was 4,920,000 copies/mL, with 237 CD4+ T lymphocytes/μL. Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate was started. By the following day the patient’s body temperature had normalized and overall laboratory findings had improved significantly (Fig. 4). On hospital day 21, he was switched from intravenous dexamethasone to oral prednisolone with a tapering plan, and was discharged without complications.

**DISCUSSION**

The most common symptoms in HLH patients are fever and progressive hepatosplenomegaly [6]. Bleeding is also a common manifestation. Thrombocytopenia and coagulopathy from liver invasion are possible explanations for the bleeding episodes in HLH patients [2]. When lymphohistiocytes invade the gastrointestinal wall ulcerative lesions develop, leading to gastrointestinal bleeding. Transmural lymphohistiocytic infiltration of macrophages was observed in some case reports [7]. Unfortunately, we could not obtain duodenal tissue in this case because of the possibility that its removal would promote bleeding. According to a literature review, most gastrointestinal bleeding cases in HLH patients result in death (12 deaths in 18 cases) [8].

Most reported cases of HLH with HIV infection are triggered by concomitant opportunistic infections and malignancies, rather than HIV itself [9]. Table 1 showcases of HIV-triggered HLH worldwide written in English [5, 10-18]. Fever was the most common clinical manifestation (100%, 11/11), followed by lymphadenopathy (72.7%, 8/11), splenomegaly (54.5%, 6/11) and hepatomegaly (36.4%, 4/11); no case presented with bleeding tendency except our case. The median CD4+ T lymphocyte was 98 cells/μL (range: 13-309) and most of cases (72.7%, 8/11) had lower than 200 cells/μL at the time of diagnosis. It means that HIV-triggered HLH has been rarely found in early-stage HIV infection.
In the present case the patient’s overall symptoms were improved by immunomodulation therapy (high-dose dexamethasone), but complete clinical recovery was only achieved by HAART. As mentioned previously, HLH is the result of an extraordinarily excessive immune response, and therefore the goal of treatment is to control life-threatening inflammation [1]. Corticosteroids, with or without cytotoxic drugs that suppress cytokine release, are commonly used to treat HLH [6]. Control of triggering, and removing stimuli that induce immune responses, are also important in treating secondary HLH [6]. There are several reports of dramatic clinical improvement in secondary HLH triggered by HIV infection after initiation of HAART [5, 16-18].

As the incidence of newly infected HIV patients is gradually increasing in Korea [19], clinicians may encounter more HLH cases among HIV patients in the near future. They should not overlook HIV infection as a possible trigger of secondary HLH. In such cases, proper HAART is the core treatment.

REFERENCES


