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LETTER TO THE EDITOR

# An infant with severe combined immunodeficiency, osteopetrosis, chromosomally integrated herpesvirus-6 infection, and hemophagocytic syndrome: What are the links?

**To The Editor**:

Osteopetrosis (OP) is a rare and heterogeneous group of skeletal dysplasias, characterized by increased bone mineral density secondary to poor bone resorption by dysfunctional/absent osteoclasts with variable clinical spectrum, including pancytopenia.[1] Generally considered to be an inherited disease, a genetic etiology can be established in approximately 90% of cases.[2] Animal experimentation however, has established both genetic and infectious pathways of etiopathology.[3]

Human herpesvirus-6 (HHV-6) is a DNA virus with unique ability to integrate into the human genome. Congenital viremia occurs in approximately 1% of the population secondary to chromosomally integrated HHV-6 (ciHHV-6) of parental origin; this form is prone to reactivation during immunodeficiency states.[4] HHV-6 can be associated with hemophagocytic syndrome (HPS).[5] The implementation of newborn screening (NBS) for severe combined immunodeficiency (SCID) in the United States has resulted in earlier detection and better prognosis.[6] Allogeneic hematopoietic stem cell transplantation (HSCT) is a curative treatment for SCID and restores hematolymphoid system in severe OP. Here, we report an infant with SCID, OP, ciHHV-6 infection, and HPS treated successfully with allogeneic HSCT.

A 10-day-old male child with a positive NBS for SCID and persistent thrombocytopenia was transferred for suspected leukemia due to immature cells in the periphery, which were shown to be nonclonal CD34-positive cells that were increased in number with absent T and natural killer (NK) lymphocytes by flow cytometry at our hospital (Figure 1A). A pathogenic variant in the interleukin-2 receptor (IL-2R) gamma chain gene confirmed [c.225_226insTGCT (p.Ser26Cysfs*2)] X-linked SCID (T-B+NK-)the diagnosis.

Repeated bone marrow aspirations were attempted to evaluate thrombocytopenia but yielded unsatisfactory samples with very few monocytes and hemophagocytic histiocytes. Subsequently, the patient developed fever and pancytopenia with elevated ferritin (1251 ng/mL) and LDH (457 IU/mL) levels and was diagnosed with HPS (Figure 1B, C). Serum soluble sIL-2R level (<31.2) was not elevated. Dexamethasone therapy resulted in resolution of fever. No variants were detected in primary hemophagocytic lymphohistiocytosis genes.

Based on the findings in skeletal survey and high circulating CD45-dim/CD34-positive hematopoietic stem cells (13%), OP was suspected (Figure 1A and Figure S1A).[7] Bone and marrow biopsy sample obtained by orthopedics showed findings consistent with OP. MRI of orbits/brain/brainstem was negative.[8] A gene panel evaluating several known OP genes and whole exome sequencing did not reveal any pathogenic variants for OP. Investigating for HPS etiology revealed HHV-6A viremia in blood and cerebrospinal fluid, with positive ciHHV-6 test.

At the age of 5 months, unrelated 10/10-matched donor HSCT was performed following fludarabine 1.2 mg/kg/dose on days −9 to −4, busulfan targeting 65 mg/L × h equates to an area under the curve (AUC) of 5278 $\mu$mol × min/L per dose on days −6 to −4 for a cumulative AUC of 15 834 $\mu$mol × min/L and thymoglobulin 2.5 mg/kg/dose on days −5 to −3 conditioning with a mononuclear cell dose of $11.35 \times 10^8$/kg and CD34+ cell dose of $7.38 \times 10^6$/kg and graft versus host disease (GvHD) prophylaxis with mycophenolate and tacrolimusat. Neutrophil engraftment was established on day +15. Posttransplant course was complicated by worsening HHV-6 viremia, moderate veno-occlusive disease of the liver (VOD), and significant transplant-associated thrombotic microangiopathy (TA-TMA), despite being on defibrotide prophylaxis for reported high-risk VOD in OP.[9] Due to increasing HHV-6 copies, the patient was treated with foscarnet with subsequent decreasing viral load. Steroid therapy continued beyond day +100 due to mild skin GvHD.

The patient achieved complete hematopoietic and immune function recovery with significantly lower and stable levels of HHV-6. Repeat radiologic evaluation showed improvement in osseous mineralization along with normal hearing test, ophthalmological examination, and orbital/brain MRI findings (Figure S1B). The patient continues to have mild renal insufficiency as a sequela of TA-TMA, has normal development except speech delay, and shows no evidence of OP 1 year from HSCT.

The patient's initial presentation, development of subsequent symptoms, and investigations leading to series of diagnosis, and interplay between all the conditions resulting in an atypical presentation, are interesting to note in this case. Since the patient had severe lymphopenia secondary to SCID, we preferred to use the term HPS. Severe T and NK lymphopenia with defective IL-2R may also account for the lack of elevated sIL-2R.[10] In addition to SCID, it is possible that congenital HHV-6 infection could have contributed to HPS development similar to a single reported case of ci-HHV-6A reactivation in a patient with X-linked SCID and HPS.[11] HSCT was the appropriate therapeutic modality for the conditions the patient had: SCID, osteopetrosis, and

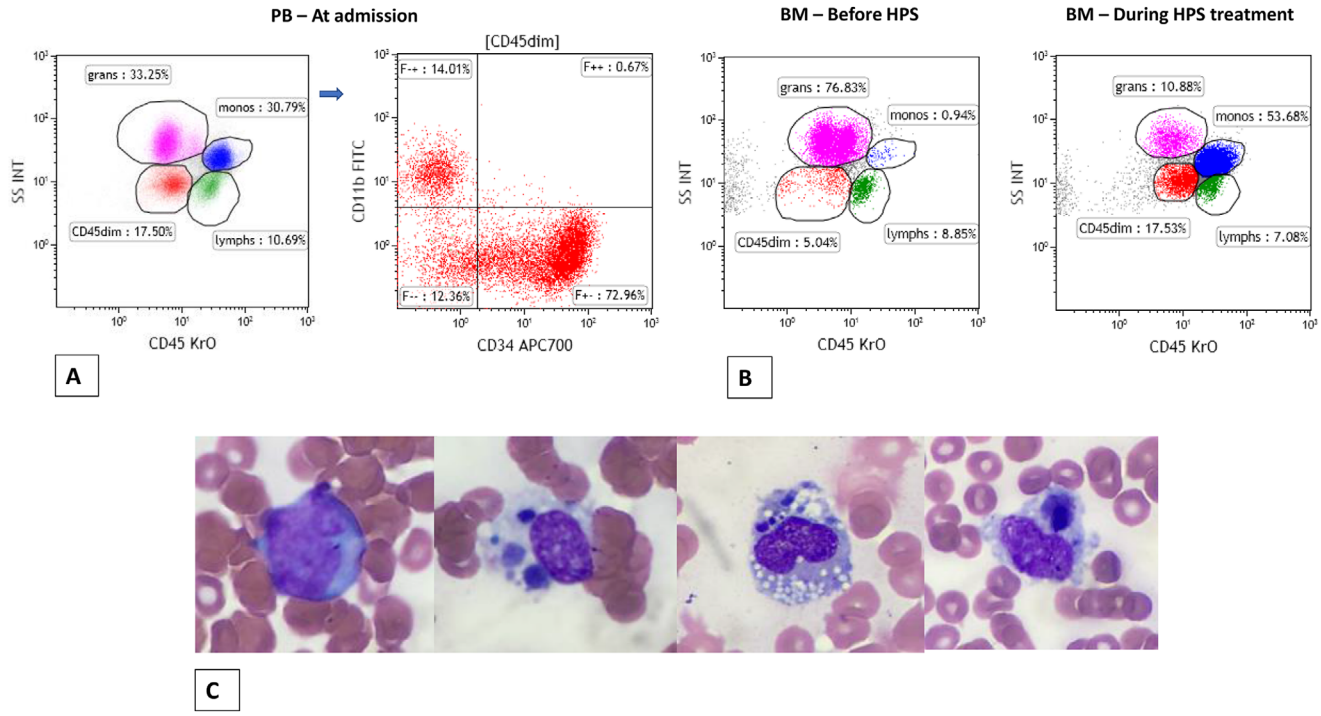


**FIGURE 1** A, Peripheral blood flow cytometric analysis of peripheral blood nuclear cells. Circulating immature cells are located in the CD45-dim population constituting 17.5% of the cells run on the left histogram. CD34-positive and CD11b-negative population makes up 72.9% cells of the gated immature population consistent with hematopoietic stem cells (13%) in the peripheral blood. **B,** Bone marrow aspirate flow cytometric analysis show presence of granulocyte population prior to development of hemophagocytic histiocytosis in the significantly acellular sample and increase of monocytic/histiocytic cells during early days of HPS treatment. **C,** There was relative prominence of monocytes (1) and hemophagocytic histiocytes (2–4) on extremely hypocellular Wright/Giemza-stained bone marrow aspiration smears (100×)

HPS. Post-HSCT course was interesting with almost simultaneous development of VOD and TA-TMA, even though the patient was on defibrotide prophylaxis. Whether ciHHV-6 infection played a role in this is unclear.[12]

We would like to propose a hypothesis linking ciHHV-6 and osteopetrosis for discussion. Multiple animal models have suggested a viral etiology for osteopetrosis in different species.[3,13,14] Although retroviruses are RNA viruses, they resemble herpesviruses in their ability to integrate into the human genome and be transmitted via Mendelian inheritance. Osteopetrosis and immunosuppression was reported in newborn kittens infected with feline leukemia virus that bore a marked resemblance to autosomal dominant OP in humans.[3] Additionally, retroviruses were isolated in adults with benign osteopetrosis.[13]Infection with HHV-6 can cause bone marrow suppression in immunocompromised individuals.[15] It is possible that ciHHV-6 with lack of T-cell immunity could have led to viremia in utero, which in turn had caused bone marrow failure with decreased/absent osteoclast development resulting in dense bone disease. Decreasing maternal anti-HHV-6 antibodies might have led to worsening viremia, then to HPS. In conclusion, the presence of X-linked SCID and ciHHV-6 infection might have been co-operational in the development of OP and HPS.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest

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