CASE REPORT

Parvovirus B19-induced hemophagocytic lymphohistiocytosis: Case report and review of the literature

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Abstract
HLH is a catastrophic and likely underdiagnosed pathology with multiple triggers including infection. PVB19 can cause persistent marrow infection leading to HLH despite negative acute serologic markers making timely diagnosis difficult. Increased awareness of PVB19-HLH is warranted given its potentially lethal nature and the careful interpretation required with serologic markers.

KEYWORDS
bone marrow, hemophagocytic lymphohistiocytosis, Parvovirus B19, viral serology

1 CASE PRESENTATION

Hemophagocytic lymphohistiocytosis (HLH) is an inflammatory disorder that in adults is typically a complication of infection, malignancy, or rheumatologic disease. Rarely, patients develop Parvovirus B19-induced HLH (PVB19-HLH). A 51-year-old female with HLH demonstrated bone marrow positivity for PVB19 DNA suggesting PVB19-HLH. Despite steroids and chemotherapy, the patient passed away.

A 51-year-old female from Indonesia (last visit in 2012) with a history of papillary thyroid cancer post-thyroidectomy/iodine ablation presented with fever, cough, and 6.4 kg unintentional weight loss over the course of 1 month. Admission laboratories were significant for hemoglobin 8.1 g/dL (Range 12-16 g/dL) and ferritin 1159 ng/mL (Range 4.6-204 ng/mL). Admission platelets and leukocyte counts were within normal limits. Temperature was >39.5°C though physical examination was unremarkable including no evidence of gastrointestinal bleed to explain anemia. Imaging revealed no organomegaly or evidence of malignancy; however, nodular pulmonary opacification suspicious for pneumonia prompted antibiotics. Blood smear was negative for schistocytes, and flow cytometry was negative for blasts. Rheumatologic workup including antinuclear antibody, rheumatoid factor, dsDNA testing and complements were within normal limits. During the first 5 days of admission, the patient remained persistently febrile prompting broadening of her antibiotic regimen, her anemia worsened necessitating transfusion, and thrombocytopenia developed. Subsequent bronchoscopy including cultures was unremarkable for an infectious etiology. Multiple sets of blood cultures returned negative while Parvovirus serology was significant for a positive IgG, negative IgM, and negative DNA PCR. By hospital day 7, the patient developed new oxygen requirement and became hemodynamically unstable necessitating ICU transfer.
Ferritin was rechecked and had increased to 3727 ng/mL raising concern for HLH. CT and ultrasound imaging demonstrated no evidence of thyroid malignancy recurrence. Triglycerides were elevated to 425 mg/dL (range <150 mg/dL) while abdominal ultrasound demonstrated splenomegaly. Bone marrow examination demonstrated hemophagocytosis and nuclear inclusions suggesting Parvovirus infection thus raising concern for PVB19-HLH. Antibiotics were discontinued, and dexamethasone 10 mg/m² was started on hospital day 12 with subsequent defervescence; however, her cytopenias persisted and by hospital day 16 the patient’s respiratory status declined necessitating intubation. Fevers recurred prompting reintroduction of antibiotics and repeat bronchoscopy including cultures was again unremarkable. Cyclosporine A 200 mg twice daily was started with dose up-titration to 250 mg twice daily. sCD25 returned markedly elevated at 98,500 pg/mL (Range <1033 pg/mL) while qualitative bone marrow PVB19 DNA PCR returned positive on hospital day 19 consistent with PVB19-HLH. A 5-day course of intravenous immunoglobulin (IVIG) 0.4 g/kg was completed with subsequent clinical improvement, successful extubation, and increased hemoglobin and platelet values. Cyclosporine A was discontinued while the patient remained on dexamethasone taper and was transferred out of the ICU. By hospital day 26, the patient clinically continued to improve however remained intermittently febrile with fluctuating blood counts and increased ferritin values up to 13,684 ng/mL prompting discussion of adding etoposide, however the patient remained clinically stable and by hospital day 30 ferritin had down-trended without new intervention to 8084 ng/mL. On hospital day 35, the patient began to develop recurrent dyspnea with a repeat ferritin of 15,658 ng/mL prompting addition of etoposide 150 mg/m². By hospital day 36, the patient became hemodynamically unstable and acidotic prompting a second transfer to the ICU. Despite broad-spectrum antibiotics, fluid resuscitation, and vasopressor support, the patient eventually passed away.

### TABLE 1

| Hemophagocytic lymphohistiocytosis 2004 diagnostic criteria⁹ |
|---------------------------------------------------------------|
| 1) Fever >38.5°C                                             |
| 2) Splenomegaly                                              |
| 3) Cytopenias (two of three lineages)                        |
| - Hemoglobin <9 g/dL                                         |
| - Platelets <100 x 10^9 g/L                                  |
| - Neutrophils <1 x 10^9 g/L                                  |
| 4) Hypertriglyceridemia >265 mg/dL and/or Hypofibrinogenemia <150 g/L |
| 5) Hemophagocytosis in bone marrow, spleen, or lymph nodes  |
| 6) Low or absent Natural-Killer Cell activity                |
| 7) Hyperferritinemia >500 ng/mL                              |
| 8) sCD25/IL-2 Receptor >2400 U/mL                            |
HLH ranging from 20% up to 85% for HLH associated with malignancies such as T‐cell lymphoma. 6,8

Current diagnostic criteria for both primary and secondary HLH are based on 2004 criteria set forth by the Histiocyte Society representing some of the common findings in the disorder (Table 1). 9 Using the HLH‐2004 criteria, demonstrating positivity for 5 criteria is considered sufficient for diagnosis and absence of any one criteria, including hemophagocytosis, does not exclude the diagnosis. Of note, these criteria were created specifically for the pediatric population and do not take into account other laboratory findings common in adult HLH patients such as elevated inflammatory markers, increased lactate dehydrogenase values, transaminitis and hepatic dysfunction, encephalopathy, and coagulopathy. 5,9 As a result, other authors have proposed alternative diagnostic criteria such as the HScore recently validated in adult patients with secondary HLH. 10 The HScore uses additional criteria such as immunosuppression and AST value to calculate a probability score between 0 and 337 with values >169 felt to accurately classify 90% of secondary HLH patients. 10

Using both the HLH‐2004 and HScore as diagnostic tools, our patient met 7/8 HLH‐2004 criteria (fever, splenomegaly, cytopenias, hypertriglyceridemia, hyperferritinemia, hemophagocytosis, and elevated sCD25) and an HScore of 264 with reported >99% probability of HLH.

Regardless of the underlying etiology for HLH, immune system hyperactivity leads to excessive release of inflammatory mediators including tumor necrosis factor-alpha (TNF‐α), interleukin‐6 (IL‐6), and interferon‐gamma (IFN‐γ) producing a cytokine storm that leads to macrophage and T‐cell activation and subsequently the clinical signs and symptoms of HLH. 6,11 Given our patient developed HLH in the setting of persistent PVB19 marrow infection, here we focus on viral etiologies of secondary HLH, also known as viral‐associated hemophagocytic syndrome (VAHS).

Viral‐associated hemophagocytic syndrome was first noted in 1979 which subsequent literature conflictingly describes both as a rare disease carrying >30% mortality as well as an underdiagnosed yet benign clinical entity. 12‐14 The underlying virion may have implications for prognosis and management thus some authors recommend extensive diagnostic workup. For example, treatment recommendations for EBV‐VAHS include corticosteroids, IVIG, etoposide, and rituximab. 15 While VAHS is most commonly associated with EBV, other implicated viruses include CMV, HIV, Herpes Simplex, and rarely PVB19. 16

PVB19 is a single‐stranded DNA erythrovirus with a tropism for bone marrow progenitor cells 17,18 producing characteristic bone marrow findings as demonstrated in our patient (Figure 1). The PVB19 genome produces the nonstructural protein (NS1) and capsid proteins VP1/VP2 which facilitate viral entry into marrow cells. 19,20 PVB19 infection is ubiquitous, with 50% of adolescents and upwards of 80% of the elderly population demonstrating evidence of serologic conversion (as noted by anti‐PVB19 IgG). 17,18,20 PVB19 infection can be diagnosed by detection of either serum IgM/ IgG or by DNA PCR. However, due to PVB19 tropism for the marrow utilization of serum samples to document clearance of infection is considered less sensitive than using bone marrow samples. 18 In a study looking at detection of PVB19 antibodies and DNA in the serum and bone marrow, 112 patients demonstrated IgG positivity and negative IgM with 4 patients additionally demonstrating positivity for PVB19 DNA in the bone marrow but not the serum. 18 These authors concluded that in low‐grade and chronic infections the serum viral copy number may be so low as to be undetectable while the marrow remains positive for PVB19. 18 This population of immunocompetent individuals who develop chronic marrow infection as demonstrated by qualitative DNR PCR in the absence of positive serum DNA PCR or IgM are referred to as “persistently infected” and have been described as exhibiting the same fever and cytopenias that characterize HLH. 21,22

PVB19 is associated with a wide array of clinical manifestations depending on the immune status of the host. Healthy individuals acutely infected with PVB19 are known to develop erythema infectiosum, arthropathy, and transient anemia. 21,22 Immunosuppressed patients infected with PVB19 may develop persistent bone marrow suppression, vasculitis, myocarditis, and thrombotic microangiopathy. 16,23 Given the relationship between PVB19 infection and cytopenias in patients with history of malignancy, PVB19 infection can be mistaken for cancer recurrence. 17 This was an initial concern with our patient however thorough evaluation of the thyroid...
There is suggestion that despite currently being considered specific pharmacologic intervention as well as having a relatively benign course demonstrating recovery without intervention,11,23,27 contract with PVB19-HLH have conflictingly been described as having increased susceptibility to secondary HLH.11 This further suggests a possible genetic predisposition for development of secondary HLH, and while unproven may have contributed to our patient to developing PVB19-HLH.

Compared with other etiologies of secondary HLH, patients with PVB19-HLH have conflictingly been described as having a relatively benign course demonstrating recovery without specific pharmacologic intervention as well as having increased mortality compared to other HLH etiologies.28 There is suggestion that despite currently being considered rare, PVB19-HLH may actually be underdiagnosed.12,13,27 Of a Japanese study of 567 patients with HLH, 163 were found to have EBV-HLH compared to three with PVB19-HLH.22 Two case reports of transplant patients developing PVB19-HLH describe recovery despite immunosuppression.23,29 Similarly, 2 cases of PVB19-HLH in pregnancy describe females who recovered and delivered healthy children while 7 cases of PVB19-HLH in patients with underlying hematologic aberration exhibited recovery either with corticosteroids or no specific intervention.12,26,32-35 Eleven cases of PVB19-HLH in reportedly healthy individuals were found, where eight patients recovered either with steroids or no treatment, while the other three suffered from multiorgan dysfunction before passing away despite steroids, IVIG, and/or etoposide.16,27,36-38 Only 9 cases actually described meeting five or more diagnostic criteria: Six of these patients recovered with either no intervention, steroids, and/or IVIG while the other three succumbed to their disease.27,29,36-40

No specific antiviral drug currently exists directed toward PVB19, and while healthy adults often require only supportive care, IVIG has been shown to increase reticulocyte count and hemoglobin level.41 Of PVB19-HLH patients who received IVIG (including the current case), four eventually succumbed to disease complications, two were solid-organ transplant recipients who recovered, and a single patient had multiple myeloma whose outcome was not discussed.23,29,36,39,41,42 Unfortunately, treatment of PVB19-HLH and VAHS overall remains challenging. Treatment regimens for HLH are again based on the HLH-94 and HLH-2004 protocols designed for pediatric populations and typically include some combination of etoposide, corticosteroids, cyclosporine A, IVIG, and allogeneic stem cell transplant.9,43 However, while etoposide-based regimens have demonstrated enhanced survival in pediatric patients with primary HLH, data regarding the survival benefit to etoposide in adult patients is inconsistent with authors describing alternative therapeutic options such as doxorubicin-based regimens, plasma exchange, anti-CD52 therapy with alemtuzumab, and anti-IL-6 therapy with tocilizumab.9,44 For PVB19-HLH and VAHS patients, published interventions include antivirals, IVIG, immunomodulatory agents, and corticosteroids; however, these have produced variable results.3,4,7 Indeed, while at different points our patient received IVIG, cyclosporine A, corticosteroids, and etoposide she eventually suffered a terminal decline.

CONFLICT OF INTEREST
None declared.

AUTHOR CONTRIBUTION
JK: is an internal medicine resident, provided direct patient care, and served as the primary author of manuscript. SM: is a hematology/oncology fellow, provided direct patient care, and served as the primary author of manuscript. GF: is a pathology resident, provided pathology images included in the manuscript, and provided guidance with paper direction and edits of the manuscript. ML: is a hematology/oncology attending physician, provided direct patient care, and oversaw the manuscript. EK: is a pulmonary/critical care attending physician, provided direct patient care, and provided guidance with paper direction and edits of the manuscript.

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