

Does Viral Hemorrhagic Fever Represent Reactive Hemophagocytic Syndrome?

The recent Ebola virus disease (EVD) outbreak is the largest in our planet's history. The epidemic is centered in West Africa, but isolated cases are being recognized across continents and represent a global health crisis¹. The mortality rate, once infected in non-hospitalized patients, is near 70%². Over 11,000 individuals have died in the recent outbreak, and this likely represents an underreported figure. In addition to the ever-rising death toll, children in West Africa are being orphaned at an alarming rate. With no proven vaccine or curative therapy currently available and the possibility for spread to tens of thousands of individuals or more, there is a desperate and urgent need for novel therapy to combat this deadly disease, yet clinical trials are just getting under way.

Clinical Features of Viral Hemorrhagic Fever (VHF)

Ebola virus infection, following an incubation period of 2 to 21 days, is clinically characterized initially by fever, myalgia, headache, weakness, and abdominal pain. This is frequently followed by vomiting, diarrhea, and occasionally by bruising and bleeding (about 1 in 5 infected); thus the terminology, Ebola hemorrhagic fever.

The hemorrhagic complications seen in Ebola virus infection are also described in other specific virus families by the US Centers for Disease Control, including arenaviruses, filoviruses, bunyaviruses, and flaviviruses; hence, the term viral hemorrhagic fever is used to describe the severe multiorgan dysfunction syndrome (MODS) in a substantial number of infected individuals³. VHF shares striking similarities with hemophagocytic syndromes (HPS), both familial hemophagocytic lymphohistiocytosis (HLH) and reactive hemophagocytic syndrome (rHPS, also called macrophage activation syndrome, or MAS), which include the following: prolonged fever, coagulopathy, hyperferritinemia, liver enzyme elevations, increased serum interleukin 1 (IL-1) levels, thrombocytopenia, and central nervous system (CNS) dysfunction^{4,5} (Table 1)⁶. Moreover, it has recently been elegantly shown in samples from the 2000–2001 Ebola outbreak of Sudan virus-associated VHF that hyperferritinemia, a hallmark of rHPS, was associated with hemorrhage and death⁴.

Like Ebola virus, rHPS has been reported in association with other hemorrhagic fever viruses, such as Crimean-Congo and Dengue, with similar clinical (e.g., MODS including CNS dysfunction and coagulopathy)^{5,7,8} and pathologic findings (e.g., hemophagocytosis)^{9,10}. As in Ebola virus

Table 1. Similarities between hemophagocytic lymphohistiocytosis (HLH) 2004 criteria and features of viral hemorrhagic fever (VHF). Adapted from Chatham and Cron. *The Rheumatologist* 2014;8:1,21–23⁶; with permission.

HLH-04 Criteria	Features of VHF
Fever	Routinely
Splenomegaly	Sometimes
Bicytopenia or pancytopenia	Frequently
Hypertriglyceridemia or hypofibrinogenemia	Both have been reported for some hemorrhagic fever viruses
Hemophagocytosis on biopsy	Yes, for the viruses studied
Hyperferritinemia (> 500 ng/ml)	Yes, often > 10,000 ng/ml
Elevated soluble CD25	Yes, for the viruses studied
Absence of decreased natural killer cell function	Poorly studied to date

infection, hyperferritinemia has been observed to be a marker of hemorrhagic manifestation (and adverse outcome) in Dengue as well¹¹. Collectively, features of VHF are seen in a substantial fraction of patients with certain viral illnesses such as Ebola virus, Dengue fever, Crimean-Congo fever, and other similar viruses. The clinical-pathological characteristics of the corresponding hemorrhagic fevers demonstrate striking resemblance with rHPS complicating viral illnesses. Despite the nonspecific nature of these findings, the constellation of these manifestations taken together is highly suggestive of rHPS. Thus, it can be speculated that VHF may in fact represent rHPS complicating the underlying viral illness.

Pathophysiology of Hemophagocytic Syndromes

Our basis of understanding hemophagocytic syndromes, HLH and rHPS, is primarily derived from the study of familial HLH. Patients with familial HLH have homozygous or compound heterozygous defects in cytotoxic granule function through either defective granule contents, e.g. perforin, or defective granule transport and fusion machinery^{12,13}. Work in genetic mouse models of familial HLH has led to a conceptual paradigm wherein defective cytotoxic killing by CD8 T cells and natural killer cells during infection leads to an inability to clear infection, and subsequent accumulation of infectious antigen^{14,15}. This accumulation of antigen results in overstimulation of the frustrated lymphocytes, copious release of cytokines (a cytokine storm), and the resulting multiorgan pathology¹³. Such situations may arise when cytotoxic granule function is genetically intact as well¹⁶. Additionally, patients with systemic lupus erythematosus, systemic juvenile idiopathic arthritis, and

other chronic inflammatory diseases may have more subtle abnormalities in cytotoxic immune cell function, perhaps exacerbated by haploinsufficient or hypomorphic genetic lesions in the perforin pathway¹³. These same patients are at risk for developing rHPS given the appropriate triggers as well.

Importantly, not all patients with rHPS demonstrate defects in cytotoxic killing, suggesting other mechanisms can lead to cytokine storm and HPS as well. For instance, in mice, excessive Toll-like receptor 9 stimulation can lead to a perforin-independent — and indeed lymphocyte-independent — cytokine-driven HPS¹⁶. Given the clinical overlap between many features of VHF and rHPS, it is intriguing to speculate whether similar pathophysiology is at play at least in part in VHF. This might be conceived as occurring as a result of excessive immune activation, as in the Toll-like receptor 9 model, or perhaps due to a subset of patients with insufficient cytotoxic cell activity, leading to viremia and resultant cytokine storm, suggested for some systemic juvenile idiopathic arthritis patients with MAS¹².

Implications for Treatment of VHF as rHPS

Traditional treatment protocols for familial HLH presenting during infancy differ from management options for rHPS, and include etoposide-based chemotherapy, followed by bone marrow transplantation. This has lowered the 5-year mortality rate from 100% to about 45%. By comparison, in general, therapy for children with rHPS includes a less toxic immunosuppressive/immunomodulatory approach, frequently with high-dose corticosteroids and cyclosporine. The therapeutic guidelines in adults with rHPS who have other comorbidities remain less well defined. More recently, the development of biologic therapeutics targeting proinflammatory cytokines has allowed for additional treatment options in treating rHPS. Novel approaches to treating rHPS include targeting of tumor necrosis factor, IL-1, and IL-6 pathways^{12,17}. The most well-reported biologic agent treatment responses for rHPS focus on the use of anakinra, a recombinant human IL-1 receptor antagonist (IL-1Ra)¹².

It is well known in the sepsis literature that the host immune response rather than the pathogen is largely responsible for MODS¹⁸. Nevertheless, immunosuppressive treatment paradigms for familial HLH and rHPS struggle with the fact that infection is often a trigger of disease, as well as a comorbidity of treatment. Immune modulation is often required in the face of infection to prevent mortality from the primary immune dysfunction. In the case of Dengue virus-induced rHPS, there are multiple reports of corticosteroids and intravenous immunoglobulin (IVIG) used to successfully walk the fine line between infection and immune dysfunction^{19,20}. Similarly, 12 patients with Crimean-Congo hemorrhagic fever were successfully treated with high-dose corticosteroids and IVIG²¹. Treating VHF as rHPS strikes at

the epitome of this balance, particularly considering that Ebola virus causes a suppression of interferon-induced immunity through viral protein 24 binding to STAT1 and antagonizing interferon signaling²².

Whether Ebola virus infection will respond to immunosuppression like other VHF viruses, however, is less clear. For example, massive lymphocyte apoptosis has been reported during Ebola infection, questioning the potential benefits of further suppressing the lymphocyte population²³. There are also data reporting increased proinflammatory cytokine levels in asymptomatic compared to symptomatic Ebola-infected individuals²⁴, as well as fatal cases of Ebola having lower levels of IL-1 compared to survivors²⁵. In this same report, antiinflammatory mediators, such as IL-1Ra and IL-10, were associated with poor prognosis²⁵. Nevertheless, it is possible that the increased serum levels of IL-1Ra and IL-10 reflect the immune system's attempt to dampen the overexuberant immune response in the sickest Ebola-infected patients experiencing MODS. Indeed, blockade of IL-10 was required to demonstrate hemophagocytosis in a murine model of rHPS¹⁶. Moreover, the concept of immune suppression of Ebola VHF has been recently considered by others²⁶.

In considering VHF as a viral infection complicated by rHPS, prudent choice of immune modulation would be of utmost importance. Borrowing from the rHPS experience, IL-1 blockade is emerging as an efficacious intervention that has not demonstrated any increased infectious risk or mortality in clinical trials of sepsis²⁷. Although the beneficial role of anticytokine therapy targeting IL-1 in rHPS has yet to be formally validated in clinical trials, the efficacy and safety of this intervention in a disorder associated with up to 60% reported mortality has nonetheless become increasingly recognized²⁸. There is now sufficient clinical and laboratory evidence that VHF may reflect viral-induced rHPS. It therefore follows that using a targeted, low infectious risk immunomodulatory approach, such as short term IL-1 blockade and/or IVIG and corticosteroids, might be an unrecognized opportunity to alter the outcome of this disease²⁶. Indeed, use of immunomodulatory versus aggressive chemotherapeutic dosing was associated with increased survival in a large cohort of rHPS patients²⁹. Secondary consideration of the potential use of other immunomodulatory approaches for rHPS, such as IL-6 blockade or other cytokine pathways that are emerging from other research models, may play a role in our armamentarium as well^{17,30}.

Given an expanding Ebola epidemic in which mortality nears 70%, a novel approach in management is worthy of investigation, particularly for those individuals who have VHF and features of rHPS. In this case, incorporating treatment of the overly exuberant host immune response to the pathogen as part of the supportive care strategy may provide an opportunity to substantially decrease mortality.

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