Editorial

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 crisis[1]. 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 individuals[3]. 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 death[4].

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 infection, hyperferritinemia has been observed to be a marker of hemorrhagic manifestation (and adverse outcome) in Dengue as well[11]. 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.

Table 1. Similarities between hemophagocytic lymphohistiocytosis (HLH) 2004 criteria and features of viral hemorrhagic fever (VHF). Adapted from Chatham and Cron. The Rheumatologist 2014;8:1,21–23[6]; with permission.

HLH-04 Criteria	Features of VHF
Fever	Routinely
Splenomegaly	Sometimes
Bicytopenia or pancytopenia	Frequently
Hypertryglyceridemia 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

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 pathology[13]. Such situations may arise when cytotoxic granule function is genetically intact as well[16]. 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 pathway[13]. 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 HPS[16]. 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 MAS[12].

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 MODS[18]. 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 IVIG[21]. 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 signaling[22].

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 population[23]. There are also data reporting increased proinflammatory cytokine levels in asymptomatic compared to symptomatic Ebola-infected individuals[24], as well as fatal cases of Ebola having lower levels of IL-1 compared to survivors[25]. In this same report, antiinflammatory mediators, such as IL-1Ra and IL-10, were associated with poor prognosis[25]. 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 rHPS[16]. Moreover, the concept of immune suppression of Ebola VHF has been recently considered by others[26].

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 sepsis[27]. 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 recognized[28]. 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 disease[26]. Indeed, use of immunomodulatory versus aggressive chemotherapeutic dosing was associated with increased survival in a large cohort of rHPS patients[29]. 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.

RANDY Q. CRON, MD, PhD,
Professor, Department of Pediatrics,
University of Alabama at Birmingham,
Birmingham, Alabama;
EDWARD M. BEHRENS, MD,
Assistant Professor,
Department of Pediatrics,
University of Pennsylvania;
BITA SHAKOORY, MD,
Assistant Professor,
Department of Medicine,
Temple University, Philadelphia, Pennsylvania, USA;
ATHIMALAIPET V. RAMANAN, FRCPCH, FRCP,
Professor, Department of Paediatrics,
Bristol Royal Hospital for Children, Bristol, UK;
WALTER W. CHATHAM, MD,
Professor, Department of Medicine,
University of Alabama at Birmingham, Birmingham, Alabama, USA.
Address correspondence to Dr. R.Q. Cron, Children's of Alabama, Division of Pediatric Rheumatology, 1600 7th Ave. South, CPP #M210, Birmingham, Alabama 35233-1711, USA. E-mail: rcron@peds.uab.edu

REFERENCES

1. Kalra S, Kelkar D, Galwankar SC, Papadimos TJ, Stawicki SP, Arquilla B, et al. The emergence of ebola as a global health security threat: from 'lessons learned' to coordinated multilateral containment efforts. J Glob Infect Dis 2014;6:164-77.
2. Cohen J. Saving lives without new drugs. Science 2014;346:911.
3. Peacock G, Uyeki TM, Rasmussen SA. Ebola virus disease and children: what pediatric health care professionals need to know. JAMA Pediatr 2014;168:1087-8.
4. McElroy AK, Erickson BR, Flietstra TD, Rollin PE, Nichol ST, Towner JS, et al. Ebola hemorrhagic fever: novel biomarker correlates of clinical outcome. J Infect Dis 2014;210:558-66.
5. Minoia F, Davi S, Horne A, Demirkaya E, Bovis F, Li C, et al. Clinical features, treatment, and outcome of macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a multinational, multicenter study of 362 patients. Arthritis Rheumatol 2014;66:3160-9.
6. Chatham WW, Cron RQ. Ebola: hemorrhagic fever and macrophage activation syndrome. The Rheumatologist 2014;8:1,21-23. [Internet. Accessed May 6, 2015.] Available from: www.the-rheumatologist.org/details/article/7131051/Ebola_Hemorrhagic_Fever_and_Macrophage_Activation_Syndrome.html
7. Bakir M, Ugurlu M, Dokuzoguz B, Bodur H, Tasyaran MA, Vahaboglu H. Crimean-Congo haemorrhagic fever outbreak in Middle Anatolia: a multicentre study of clinical features and outcome measures. J Med Microbiol 2005;54:385-9.
8. Rathakrishnan A, Klekamp B, Wang SM, Komarasamy TV, Natkunam SK, Sathar J, et al. Clinical and immunological markers of dengue progression in a study cohort from a hyperendemic area in Malaysia. PLoS One 2014;9:e92021.
9. Bicakci Z, Tavil B, Tezer H, Olcay L. Hemophagocytosis in a case with Crimean-Congo hemorrhagic fever and an overview of possible pathogenesis with current evidence. Turk J Pediatr 2013;55:344-8.
10. Tan LH, Lum LC, Omar SF, Kan FK. Hemophagocytosis in dengue: comprehensive report of six cases. J Clin Virol 201255:79-82.
11. Chaiyaratana W, Chuansumrit A, Atamasirikul K, Tangnararatchakit K. Serum ferritin levels in children with dengue infection. Southeast Asian J Trop Med Public Health 2008;39:832-6.
12. Ravelli A, Grom AA, Behrens EM, Cron RQ. Macrophage activation syndrome as part of systemic juvenile idiopathic arthritis: diagnosis, genetics, pathophysiology and treatment. Genes Immun 2012;13:289-98.
13. Zhang M, Behrens EM, Atkinson TP, Shakoory B, Grom AA, Cron RQ. Genetic defects in cytolysis in macrophage activation syndrome. Curr Rheumatol Rep 2014;16:439-46.
14. Jordan MB, Hildeman D, Kappler J, Marrack P. An animal model of hemophagocytic lymphohistiocytosis (HLH): CD8+ T cells and interferon gamma are essential for the disorder. Blood 2004;104:735-43.
15. Sepulveda FE, Maschalidi S, Vosshenrich CA, Garrigue A, Kurowska M, Menasche G, et al. A novel immunoregulatory role for NK-cell cytotoxicity in protection from HLH-like immunopathology in mice. Blood 2015;125:1427-34.
16. Behrens EM, Canna SW, Slade K, Rao S, Kreiger PA, Paessler M, et al. Repeated TLR9 stimulation results in macrophage activation syndrome-like disease in mice. J Clin Invest 2011;121:2264-77.
17. Maude SL, Frey N, Shaw PA, Aplenc R, Barrett DM, Bunin NJ, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med 2014;371:1507-17.
18. Angus DC, van der Poll T. Severe sepsis and septic shock. N Engl J Med 2013;369:840-51.
19. Raju S, Kalyanaraman S, Swaminathan K, Nisha A, Praisid S. Hemophagocytic lymphohistiocytosis syndrome in dengue hemorrhagic fever. Indian J Pediatr 2014;81:1381-3.
20. Ramachandran B, Balasubramanian S, Abhishek N, Ravikumar KG, Ramanan AV. Profile of hemophagocytic lymphohistiocytosis in children in a tertiary care hospital in India. Indian Pediatr 2011;48:31-5.
21. Erduran E, Bahadir A, Palanci N, Gedik Y. The treatment of crimean-congo hemorrhagic fever with high-dose methylprednisolone, intravenous immunoglobulin, and fresh frozen plasma. J Pediatr Hematol Oncol 2013;35:e19-24.
22. Zhang AP, Bornholdt ZA, Liu T, Abelson DM, Lee DE, Li S, et al. The ebola virus interferon antagonist VP24 directly binds STAT1 and has a novel, pyramidal fold. PLoS Pathog 2012;8:e1002550.
23. Wauquier N, Becquart P, Padilla C, Baize S, Leroy EM. Human fatal zaire ebola virus infection is associated with an aberrant innate immunity and with massive lymphocyte apoptosis. PLoS Negl Trop Dis 2010;4:pii:e837.
24. Leroy EM, Baize S, Volchkov VE, Fisher-Hoch SP, Georges-Courbot MC, Lansoud-Soukate J, et al. Human asymptomatic Ebola infection and strong inflammatory response. Lancet 2000;355:2210-5.
25. Baize S, Leroy EM, Georges AJ, Georges-Courbot MC, Capron M, Bedjabaga I, et al. Inflammatory responses in Ebola virus-infected patients. Clin Exp Immunol 2002;128:163-8.
26. van der Ven AJ, Netea MG, van der Meer JW, de Mast Q. Ebola virus disease has features of hemophagocytic lymphohistiocytosis syndrome. Front Med 2015;2:4.
27. Opal SM, Fisher CJ Jr., Dhainaut JF, Vincent JL, Brase R, Lowry SF, et al. Confirmatory interleukin-1 receptor antagonist trial in severe sepsis: a phase III, randomized, double-blind, placebo-controlled, multicenter trial. The Interleukin-1 Receptor Antagonist Sepsis Investigator Group. Crit Care Med 1997; 25:1115-24.
28. Miettunen PM, Narendran A, Jayanthan A, Behrens EM, Cron RQ. Successful treatment of severe paediatric rheumatic disease-associated macrophage activation syndrome with interleukin-1 inhibition following conventional immunosuppressive therapy: case series with 12 patients. Rheumatology 2011;50:417-9.
29. Ishii E, Ohga S, Imashuku S, Yasukawa M, Tsuda H, Miura I, et al. Nationwide survey of hemophagocytic lymphohistiocytosis in Japan. Int J Hematol 2007;86:58-65.
30. Vanden Berghe T, Demon D, Bogaert P, Vandendriessche B, Goethals A, Depuydt B, et al. Simultaneous targeting of IL-1 and IL-18 is required for protection against inflammatory and septic shock. Am J Respir Crit Care Med 2014;189:282-91.

J Rheumatol 2015;42:1078–80; doi:10.3899/jrheum.150108