

Chronic Granulomatous Disease Presenting as Hemophagocytic Lymphohistiocytosis: A Case Report

AUTHORS: Gregory Valentine, MD, Tessy A. Thomas, MD, Trung Nguyen, MD, and Yi-Chen Lai, MD

Section of Pediatric Critical Care Medicine, Department of Pediatrics, Baylor College of Medicine, Houston, Texas

KEY WORDS

chronic granulomatous disease, fungemia, hemophagocytic lymphohistiocytosis, immunocompromised host, immunomodulation

ABBREVIATIONS

CGD—chronic granulomatous disease

HLH—hemophagocytic lymphohistiocytosis

NK—natural killer

Dr Valentine compiled the pertinent clinical data for the report and drafted and revised the manuscript for submission; Dr Thomas participated in the preparation of the case report and drafted the initial manuscript in conjunction with Dr Valentine; Dr Nguyen participated in the design and concepts of the case report; and Dr Lai was primarily responsible for all aspects of the case report.

www.pediatrics.org/cgi/doi/10.1542/peds.2014-2175

doi:10.1542/peds.2014-2175

Accepted for publication Sep 18, 2014

Address correspondence to Yi-Chen Lai, MD, Jan and Dan Duncan Neurologic Research Institute, 1250 Moursund St, Suite 1225, Houston, TX 77030. E-mail: ylai@bcm.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

abstract

Chronic granulomatous disease (CGD) is a primary immunodeficiency characterized by recurrent infections and a dysregulated inflammatory response. Infection-triggered hemophagocytic lymphohistiocytosis (HLH), which manifests itself as pathologic hyperactive inflammation, has been observed in subjects with CGD. However, there have been no reports of HLH as the initial presentation with subsequent diagnosis of CGD. Furthermore, the primary therapeutic strategy for HLH focuses on immunosuppressive therapies, which limits immune-mediated tissue damage. With immunodeficiency, this therapeutic strategy may worsen the outcome. This article discusses an 8-week-old Hispanic male who presented with fever of unknown origin. The initial diagnostic evaluation demonstrated pathologic hyperactive inflammation, meeting the HLH-2004 diagnostic criteria without an identified infectious etiology. Immunosuppressive therapy was initiated, with subsequent disseminated candida septic shock and sepsis-induced multisystem organ failure. Additional evaluations ultimately established the diagnosis of CGD. We transitioned to an immune-enhancing strategy with granulocyte and immunoglobulin infusions, and intensified antifungal therapies. These interventions ultimately led to the clearance of the fungal infection and the resolution of the hyperactive inflammatory state. This case represents the first reported case of HLH as the presenting finding leading to the subsequent diagnosis of CGD. It serves as a reminder that both immunodeficiency and inflammatory disorders may share features of pathologic hyperactive inflammation and highlights the conundrum that clinicians face when treating HLH in the setting of an unresolved infection. In this case report, we demonstrate that immune-enhancing therapies may aid in the control and the clearance of the infection, thus paradoxically decreasing the pathologic hyperactive inflammatory response. *Pediatrics* 2014;134:e1727–e1730

BACKGROUND

Immune activation serves as an adaptive response against pathogens. It is finely regulated by various mechanisms such that once the pathogens are eliminated, the immune response returns to the basal state. Diverse pathologic conditions are associated with immune dysregulation manifested as persistent and hyperactive inflammation. Both immunodeficiency with unresolved infection and inflammatory disorders can present with hyperactive inflammation but with a dichotomous therapeutic approach: immune enhancement in the former and immunosuppression in the latter. Because these subjects most commonly present to the general practitioners with fever of unknown origin, early diagnostic evaluation for both possibilities by the primary care provider will greatly affect the timely initiation of appropriate therapeutic interventions.

Chronic granulomatous disease (CGD) is a primary immunodeficiency of impaired phagocyte killing.¹ Due to a defect in generating respiratory burst-derived oxidants, subjects with CGD exhibit impaired clearance of certain bacteria and fungi such as *Staphylococcus aureus*, *Nocardia*, *Aspergillus*, *Burkholderia cepacia*, and gram-negative enteric bacteria.^{1,2} Therefore, infections caused by these organisms represent the most common presentations prompting the diagnostic evaluation for CGD.³ In addition, inflammatory dysregulation can manifest as sterile granulomas^{1,2} and a higher prevalence of discoid lupus.² These findings suggest that subjects with CGD may exhibit pathologic hyperactive inflammation as a result of either persistent infection or dysregulated immune response. Accordingly, infection-triggered hemophagocytic lymphohistiocytosis (HLH) has been reported in patients with CGD with concurrent infections.⁴⁻⁹ However, there have been no reports of HLH as the presenting clinical finding leading to the diagnosis of CGD.

HLH is a syndrome of pathologic immune activation characterized by signs and symptoms of extreme inflammation. The diagnostic criteria of HLH reflect the presence of hyperactive inflammation and the immune-mediated pathology (Table 1).¹⁰ Classically, HLH is associated with inherited disorders of natural killer (NK) cells (primary HLH). Subsequently, HLH has been associated with known triggers such as rheumatologic, infectious, and oncologic disorders (secondary HLH).¹⁰ Because immune-mediated tissue damage contributes significantly to the HLH pathology and mortality, primary therapeutic strategies focus on the immunosuppressive agents with dexamethasone and etoposide to dampen the hyperactive inflammation.¹⁰ However, in situations in which the hyperactive inflammation reflects the presence of an unresolved infection due to an underlying immunodeficiency, institution of immunosuppressive therapies may worsen the outcome.

The present article reports a case of an 8-week-old Hispanic male presenting to his primary care provider with fever of unknown origin. The initial diagnostic evaluation revealed hyperactive inflammation meeting the HLH-2004 diagnostic criteria. Immunosuppressive therapy was initiated, with subsequent disseminated candida septic shock and sepsis-induced multisystem organ

failure. Additional evaluations ultimately established the diagnosis of CGD.

CASE PRESENTATION

An 8-week-old Hispanic male presented with chief complaint of fever (38.9°C) and rash on his face and neck for 10 days. He had been born at term after an uncomplicated pregnancy. The patient was hospitalized at 2 weeks of age for pneumonia and fever, symptoms that were subsequently attributed to pertussis. There was no family history of immunodeficiencies, autoimmune diseases, or early childhood deaths. Results of his newborn screening were normal. His initial physical examination was normal except for erythematous macules and papules on the face and neck. Despite extensive searches for an infectious etiology, the initial evaluation was negative for bacterial and viral pathogens. He was subsequently given intravenous immunoglobulin for suspected Kawasaki disease, with resolution of the fever and rash.

The patient's fever recurred after a transient clinical improvement with intravenous immunoglobulin. He developed pancytopenia, hypofibrinogenemia, transaminitis, and elevated ferritin of 11 783 ng/mL. His physical examination became notable for ascites, hepatosplenomegaly, and hydrops of the gallbladder. Results of a bone marrow

TABLE 1 HLH-2004 Diagnostic Criteria and Patient's Clinical Findings

HLH-2004 Diagnostic Criteria	Patient's Initial Clinical Findings
Molecular diagnosis consistent with HLH	Absent
Fever	Present
Splenomegaly	Present
Cytopenias (≥ 2 of 3 lineages)	
• Hemoglobin < 9 g/dL	5.9 g/dL
• Neutrophil $< 1 \times 10^9$ cells/L	2×10^9 cells/L
• Platelet $< 100 \times 10^9$ cells/L	90×10^9 cells/L
Hypertriglyceridemia or hypofibrinogenemia	
• Fasting triglyceride ≥ 265 mg/dL	Not performed
• Fibrinogen < 1.5 g/L	0.8 g/L
Low NK cell activity	Inadequate sample
Ferritin ≥ 500 μ g/L	11 783 μ g/L
Soluble IL-2 ≥ 2400 U/mL	17 035 U/mL
Hemophagocytosis in bone marrow, spleen, or lymph nodes	Single hemophagocyte in bone marrow biopsy

biopsy and aspiration demonstrated cytopenia, and one hemophagocytic histiocyte (within normal limits). The soluble IL-2 receptor level was elevated at 17 035 U/mL. A NK cell study was inconclusive due to an inadequate sample. The constellation of the clinical findings and laboratory data met the HLH-2004 diagnostic criteria (Table 1). Cyclosporine and dexamethasone were initiated for HLH treatment in lieu of dexamethasone and etoposide because of ongoing concerns regarding clinical instability and sepsis. The fevers subsided and the ferritin level decreased (249 ng/mL). Results of the primary HLH evaluation were negative, with normal perforin and granzyme expression and normal familial HLH genes (*MUNC*, *PRF1*, *STXBP2*, *RAB27A*, *STX11*, *SAP*, *XIAP*).

While the patient was on cyclosporine and dexamethasone, he developed disseminated *Candida lusitanae* septic shock and multisystem organ failure, with positive blood and peritoneal cultures. Results of subsequent cultures from blood, urine, cerebrospinal fluid, and peritoneum were negative for bacterial, viral, and fungal pathogens. Repeat soluble IL-2 receptor levels were still elevated at 1365 U/mL. Because of the concern for an HLH exacerbation with cyclosporine and dexamethasone, an IL-1 receptor antagonist (anakinra) was given daily as salvage therapy; there was no clinical response after 14 days of therapy at 4 mg/kg per dose. He subsequently completed 8 weeks of cyclosporine and dexamethasone induction therapy and remained on dexamethasone at the time of referral to our center for further management.

During the hospitalization, the patient developed multifocal seizures after an initially normal head MRI. After disseminated candida sepsis-induced multisystem organ failure, serial head MRIs demonstrated progressive infiltrative leptomeningeal enhancement and communicating hydrocephalus. Re-

peat cerebrospinal fluid studies demonstrated significantly elevated protein and lactate levels, leukocytosis, and low glucose levels. Results of a cervical lymph node biopsy revealed multiple granulomas with central caseating necrosis with few clusters of budding yeasts. Results of a dura biopsy showed a dense mixed lymphohistiocytic infiltrate. These findings, in conjunction with persistent fever and significantly elevated serum (1,3)- β -D-glucan, suggested persistent candida infection with fungal meningoencephalitis.

The persistent fungal infection after immunosuppression coupled with the age of the patient highly suggested the possibility of immunodeficiency as an alternative etiology. Evaluation for immunodeficiency was thus initiated on the patient's transfer to our center. T-cell phenotyping demonstrated normal NK cells (7%), CD4+ cells (57%), and low CD8+ cells (1.4%) while receiving dexamethasone. A lymphocyte proliferation assay demonstrated normal response to mitogen. Results of 2 dihydrorhodamine tests showed no uptake in neutrophil oxidative burst after phorbol myristate acetate stimulation. Whole-genome exome sequencing revealed mutation in the *CYBB* gene (C.1557delA) encoding for gp91^{phox} protein, the most commonly affected protein in the X-linked form of CGD.² *CYBA*, *NCF1*, and *NCF2* were normal. A diagnosis of CGD was therefore confirmed.

We intensified the patient's antifungal therapy with the addition of voriconazole and flucytosine along with amphotericin. We instituted immunomodulation with granulocyte infusion and intravenous immunoglobulin. The patient became afebrile concurrent with decreased serum (1,3)- β -D-glucan levels over time. His ferritin levels normalized, and his pancytopenia, hypofibrinogenemia, and transaminitis resolved. He was discharged from the hospital on γ -interferon and prophylactic antimicrobial and antifungal

therapies. Unfortunately, he sustained significant neurologic sequelae with static encephalopathy and epilepsy and therefore is currently not considered for a bone marrow transplant. HLH has not recurred for 1 year.

CONCLUSIONS

This case represents a unique initial presentation (HLH) of an uncommon disease (CGD) and a reminder that both immunodeficiency and inflammatory disorders may share features of pathologic hyperactive inflammation. This infant presented with fever of unknown origin and findings of hyperactive inflammation in the absence of pathogens. Because noninfectious inflammatory diseases constitute a common category underlying fever of known origin,¹¹ it would be reasonable to focus on these conditions as potential etiologies. However, as our case illustrates, clinicians should consider immunodeficiency even in the absence of suggestive history and laboratory findings. Early diagnostic evaluation for both immunodeficiency and inflammatory diseases will greatly affect the timely initiation of appropriate therapies.

Although infection-triggered HLH has been observed in subjects with CGD, there have been no reports of HLH as the presenting finding leading to the diagnosis of CGD. The most common presentation in both the X-linked and autosomal recessive CGD is pulmonary infection, followed by skin and organ abscesses.¹⁻³ Despite intensive searches, no pathogens were initially identified in this child. In contrast, he exhibited a constellation of findings reflecting significant pathologic hyperactive inflammation consistent with HLH.¹⁰ Because immune-mediated tissue damage contributes significantly to the HLH pathology, primary therapeutic strategies focus on early initiation of immunosuppressive agents with dexamethasone and etoposide to dampen the state of hyperactive inflammation.¹⁰ Therefore, timely initiation

of immunosuppressive therapies would be indicated to ameliorate the deleterious consequences. However, given this child's age, immunodeficiency should also be aggressively investigated before the immunosuppressive therapy. In this case, a diagnostic evaluation was initiated after the disseminated and persistent candida infection, prompting the re-examination of the clinical findings. Delineating pathologic immune activation from a normal adaptive response before initiation of immunosuppressive therapies is paramount because immunosuppression in a setting of immunodeficiency may exacerbate the infection, as was exemplified by the present case.

Although dysregulated inflammation can manifest as sterile granulomas and

discoid lupus in patients with CGD, all reported cases of HLH with overwhelming pathologic immune activation occur in the setting of persistent infection⁴⁻⁹ suggesting that impaired pathogen killing underlies the pathologic hyperactive inflammation. Interestingly, all patients who received intravenous immunoglobulin and pathogen-specific therapies survived,^{4,5,7,8} while the reported deaths occurred in patients who received either inadequate pathogen-specific therapy or immunosuppressive therapies for HLH.^{6,9} Therefore, perhaps in patients with CGD who also have infection-triggered HLH, greater focus on eliminating the infection by immune-enhancing strategies may paradoxically decrease the hyperactive inflammatory response and improve the clinical outcome. We modulated our

therapeutic goals from immunosuppression to immune enhancement and were successful in achieving control of the fungal infection without exacerbating the inflammatory response.

Immunodeficiency can present with hyperactive inflammation consistent with HLH. Therefore, early diagnostic evaluation by primary care providers for both possibilities will greatly affect the timely institution of appropriate therapeutic interventions. Immunosuppressive therapies, although effective in modulating the pathologic consequences of hyperactive inflammation, may worsen the infection. Immune-enhancing therapies may aid in the control and the clearance of the infection, thus paradoxically decreasing the pathologic hyperactive inflammatory response.

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DOI: 10.1542/peds.2014-2175 originally published online November 24, 2014;

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