CASE STUDIES
IN
CLINICAL LABORATORY SCIENCE

"Hemophagocytic Lymphohistiocytosis"
CASE 07-5

CLINICAL LABORATORY SCIENCE PROGRAM
UNIVERSITY OF NORTH DAKOTA
SCHOOL OF MEDICINE AND HEALTH SCIENCES
GRAND FORKS, ND

ACKNOWLEDGEMENTS

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TITLE: "Hemophagocytic Lymphohistiocytosis"
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Some of the information which is presented in this case study may have been revised to emphasize the role of the laboratorian.

PART A

PATIENT HISTORY

On September 11, 2006, a 23 year old female, with no remarkable health history, was admitted to the intensive care unit at a mid-size hospital. Her main symptoms included a high fever, fatigue, and cytopenic blood counts. After many tests, a preliminary diagnosis of human granulocytic Ehrlichiosis was made. The patient was released on September 14, feeling much better. However, three days later, the patient returned to the emergency room with a 107.5°F fever, severe thrombocytopenia, and hepatosplenomegaly. Urinalysis and chemistry results also indicated hemolysis and liver involvement, with severe bacterial sepsis being the most likely diagnosis.

Laboratory Results: 9/14/06

Urine HCG			
Urine HCG	Negative		
Urinalysis			
Collection	Voided		
Color	Yellow		
Clarity	Turbid	[clear]	
Glucose	Negative	[negative]	mg/dL
Bilirubin	Moderate	[negative]	
Ictotest	Positive		
Ketones	≥80	[negative]	mg/dL
Specific Gravity	1.025	[1.003-1.035]	
Hemoglobin	Moderate	[negative]	
pH	5.5	[5.0-8.0]	
Protein	≥300	[negative]	mg/dL
Urobilinogen	4.0	[0.2-1.0]	mg/dL
Nitrite	Negative	[negative]	
Leukocytes	Negative	[negative]	
Epithelial cells	3+		/hpf
Mucous	Negative		/hpf
RBCs	10-12		/hpf
WBCs	4-6		/hpf
Bacteria	3+		/hpf
Urine Culture	No Growth 2 Days.		Final: 9/13/2006
Blood Culture	No Growth 5 Days.		Final: 9/17/2006

Basic Metabolic Panel			
Bun	20	[7-22]	mg/dL
Sodium	132	[136-145]	mmol/L
Potassium	4.0	[3.6-5.5]	mmol/L
Chloride	94	[98-109]	mmol/L
CO_2	20.1	[23-33]	mmol/L
Glucose	106	[70-99]	mg/dL
Creatinine	1.2	[0.6-1.3]	mg/dL
Calcium	8.1	[8.8-10.5]	mg/dL
Hepatic Function Panel			
Albumin	3.3	[3.2-4.6]	g/dL
Alk. Phosphatase	196	[50-136]	IU/L
Total Bilirubin	3.4	[0.0-1.0]	mg/dL
Direct Bilirubin	2.8	[0.0-0.3]	mg/dL
AST (SGOT)	854	[8-42]	IU/L
ALT (SGPT)	148	[30-65]	IU/L
Total Protein	6.4	[5.9-7.6]	g/dL
Magnesium	1.7	[1.4-2.2]	mg/dL
Phosphorus	3.4	[2.5-5.9]	mg/dL
CBC			
WBC	5.3	[3.6-11.0]	K/uL
RBC	4.33	[3.80-5.20]	M/uL
Hgb	12.9	[12.0-16.0]	g/dL
Hct	36.5	[35-47]	%
MCV	84.3	[80-100]	fL
MCH	29.8	[26-34]	pg
MCHC	35.3	[32-36]	g/dL
RDW	14.7	[11.6-16.5]	
Plts	41	[150-440]	K/uL
MPV	10.5	[0.0-99.8]	fL
Manual Differential			
Neutophil %	60.0	[54-74]	%
Band %	2.0	[2-6]	%
Lymphocyte %	36.0	[22-42]	%
Monocyte %	2.0	[2-8]	%
Neutrophil Abs.	3.17	[1.5-8.5]	K/uL
Band Abs.	0.11	[0.0-0.6]	K/uL
Lymphocyte Abs.	1.91	[1.1-3.5]	K/uL
Monocyte Abs.	0.11	[0.2-0.8]	K/uL
Plt Comments:		Marked Decrease	
RBC Morphology:		Normocytic Normochromic	
WBC Morphology:		Atypical Lymphocytes Present	

The patient was transferred to a larger hospital where she was immediately placed on a gamut of five antibiotics, anti-fungal, and anti-viral drugs, to combat the unknown infectious agent. The patient showed little improvement and due to her overwhelming immune response to the drug therapy, began to show signs of multi-organ failure, and as a result began therapy with the anti-sepsis drug Xigris®. She was also placed on a ventilator, kidney dialysis, and in a medically induced coma. A bone marrow aspiration was performed and subsequent testing revealed the presence of Epstein-Barr related Hemophagocytic Lymphohistiocytosis. The patient was then started on the anti-viral drug Acyclovir and transferred to a pediatric children's hospital. Here, the patient began a course of chemotherapy and underwent testing to determine whether the form of her condition was reactive or familial. The patient was released on October 5th on an outpatient chemotherapy regimen.

DISCUSSION QUESTIONS:

1. What is Ehrlichiosis and what symptoms of this condition matched with the patient's symptoms?

2. List the abnormal laboratory test results from the patient's 9/14/06 admission, and discuss their significance.

3. The most significant side effect of Xigris® is bleeding. Why would this be of such great concern for this patient?

4. List the disease(s) most commonly involved with infection by the Epstein-Barr virus. Which cells are involved in these infections? Which cells are involved in Hemophagocytic Lymphohistiocytosis?

5. What is the significance of negative PRF1 and Munc13-4 chromosomal mutation results?

PART B

DISCUSSION QUESTIONS ANSWERED:

1. What is Ehrlichiosis and what symptoms of this condition matched with the patient's symptoms?

   Ehrlichiosis is a pathogenic infection caused by microorganism invasion of leukocytes. The infected leukocytes eventually lyse and release more organisms, continuing the infective cycle. Symptoms of Ehrlichiosis include: myalgia, anorexia, pancytopenia, lethargy, and a rash. The patient's fever, lethargy, and thrombocytopenia paralleled the symptoms of an infective agent such as Ehrlichia.

2. List the abnormal laboratory test results from the patient's 9/14/06 admission, and discuss their significance.

   Urinalysis: Bilirubin, Hemoglobin, Urlobilinogen, Ketones, Turbid
   BMP : Sodium, Chloride, CO2, Glucose, Calcium
   HFP: Alk. Phosphatase, Total and Direct Bilirubin, AST, ALT
   CBC: Platelet Count, Absolute Monocyte Count

   The Urinalysis, BMP, and HFP results all indicate an abnormal level of pathogenicity. Specifically, these results suggest some sort of hemolytic (or destructive) erythrocyte process. Secondly, the elevated liver enzymes support the physical finding of hepatosplenomegaly, and indicate liver involvement. Finally, the hematology results show an alarming thrombocytopenia.

3. The most significant side effect of Xigris® is bleeding. Why would this be of such great concern for this patient?

   The patient was severely thrombocytopenic at the time when therapy with Xigris® was being considered. The patient's low platelet count adds to the likelihood of excessive bleeding, which is a common occurrence with Xigris®.

4. List the disease(s) most commonly involved with infection by the Epstein-Barr virus. Which cells are involved in these infections? Which cells are involved in Hemophagocytic Lymphohistiocytosis?

   The Epstein-Barr virus is most commonly associated with infectious mononucleosis, but has also been associated with malignant diseases such as Burkitt's lymphoma and nasopharyngeal carcinoma. During the infective process of infectious mononucleosis, Epstein-Barr virus particles attach to B lymphocytes through a specific B-cell membrane receptor, termed CD21. However, the affected cells in Epstein-Barr related Hemophagocytic Lymphohistiocytosis are T lymphocytes, not B lymphocytes.

5. What is the significance of negative PRF1 and Munc13-4 chromosomal mutation results?

   PRH1 and Munc13-4 are the two most common gene mutations found in the familial form of Hemophagocytic Lymphohistiocytosis. Results showing neither of these two mutations, would suggest that the patient does not have the familial form of Hemophagocytic Lymphohistiocytosis, but rather a reactive form of the disease (secondary to another infection).

DISCUSSION

Hemophagocytic Lymphohistiocytosis (HLH) is a rare, but serious, disease. HLH is characterized by overactive, or overstimulated, macrophages and lymphocytes and may result in death without proper treatment (Lacz, Schwartz, & Desposito, 2006). Manifestations of HLH appear one of two ways. The first, termed primary HLH or Familial Hemophagocytic Lymphohistiocytosis (FHLH), results from an inherited chromosomal mutation (Cincinnati Children's Hospital, 2006). Specifically, individuals with immune deficiencies such as Chediak-Higashi syndrome, Griscelli syndrome, and X-linked lymphoproliferative syndrome have demonstrated an increased predisposition for FHLH (Janka & Stadt, 2005). Secondary HLH, or reactive HLH, develops sporadically, usually as a consequence of immune stimulation by an infection, immunodeficiency, or underlying malignancy (Lacz, 2006).

In both primary and secondary HLH, the disease pathogenicity is triggered by infection, usually viral, or other stimuli (Janka & Stadt, 2005). One virus in particular, the Epstein-Barr virus, appears to be a common initiator of HLH and has sparked growing concern due to its lethality when in conjunction with HLH (Imashuku et al. 1999). The disease's initiation process makes it difficult to distinguish one form from the other at the time of onset, and thus mandates genetic testing as a mandatory diagnostic criterion.

Pathophysiology

The pathophysiology of this disease revolves around the hemophagocytic capabilities errantly adopted by mononuclear cells, resulting in phagocytosis, and eventual cytopenia of platelets, white blood cells, and red blood cells (Lacz et al., 2006). It appears that the excessive activation of the immune system is overstimulated, but with opposing results of decreased immune cytolytic activity. The increased inflammatory response is caused by excessive

secretion of cytokines from activated T lymphocytes and histiocytes. Specifically, NK cells and macrophages, once activated by the viral particles, produce interferon-γ and TNF-α at an unregulated level, resulting not in increased immunity, but rather an impairment of cytolytic activity resulting in a shock-like syndrome displaying DIC and multiple organ failure (Janeway, Travers, Walport, & Schlomchik, 2005).

Despite the induced increase in numbers and activation, the cytotoxic cells involved in HLH have impaired or absent immune capabilities (Janka & Stadt, 2005). Slightly different hypotheses exist as to the exact pathyphysiology for the acquired and familial forms of HLH, and thus will be examined separately.

Epstein-Barr associated Hemophagocytic Lymphohistiocytosis.

Epstein-Barr associated HLH is the most commonly diagnosed form of acquired HLH. Although exact mechanisms of the disease's pathogenicity have yet to be established, it is suggested that high levels of activating cytokines excessively stimulate monocytes, leading to eventual uncontrolled phagocytosis.

Epstein-Barr virus is most often associated with the disease Infectious Mononucleosis (IM). During IM, EBV infects B lymphocytes by attaching to a portion of the B-cell co-receptor complex, CD21 (Janeway, et al. 2005) The infective mechanism of EBV in EBV-associated HLH differs from IM in that it is the T lymphocytes that are involved, rather than B cells (Janeway). Data from patients with EBV-associated HLH and other EBV-positive T-cell lymphomas has suggested that despite the fact that T lymphocytes lack the EBV receptor (CD21), they still harbor the EBV genome, and once infected, induce higher production of inflammatory cytokines, such as TNF-α, than other cells, leading to the eventual clinical presentation of HLH. (Fisman, 2006). The latter explanation, suggesting direct targeting of T

lymphocytes by EBV is in contrast to the more common theory that EBV-infected B lymphocytes stimulate proliferation of cytotoxic T cells, which go on to overstimulate the phagocytic immune response (Imashuku et al., 1999).

Familial HLH

FHLH1. Little is known of the mutated gene identity in FHLH1. 9q21.2-22 has been acknowledged as the abnormal mapping region in patients with the inherited FHLH1. However, disease pathophysiology remains under investigation until more data and research can be compiled.

FHLH2. A 10q21 mutation in the PRF1 gene has been identified as the causative mutation in FHLH2. PRF1 is the most frequently isolated genetic abnormality in cases of FHLH, resulting in a greater understanding of the disease mechanism. Normally, the PRF1 gene encodes for the inactive precursor form of perforin, which, upon maturation, is stored in lytic granules of NK and cytotoxic T lymphocytes (CTLs) (Trambas et al., 2005). Once the NK and/or CTLs encounter their target cell and release their granules, perforin, is able to form pores in the foreign cell, allowing for insertion of the other cytotoxic granules and eventual cell lysis (Marcenaro et al., 2006). However, the PRF1 mutation results in either complete loss of perforin, production of nonfunctional protein, or loss of functional mRNA in the perforin protein structure, thus reducing or eliminating the ability of CTLs and/or NK cells to destroy their target cells, and allowing for unregulated proliferation of the pathogen.

Recently, a newly discovered point mutation in PRF1 has also been linked to impaired NK and CTL function. This mutation, A91V, results in a loss of recognition by the antiperforin antibody, δG9, leading to the impaired ability to cleave inactive perforin to active perforin (Trambas et al., 2005). Although the role of A91V is still under investigation, the mutation

appears to be more frequently isolated in late onset HLH, and shows lethal effects when inherited in the homozygous form (Trambas).

FHLH3. The second most frequently identified acquired form of HLH, FHLH3, results from a 17q25 mutation in the *Munc13-4* gene. *Munc13-4* is also involved with the cytolytic granule release of NK and CTL cells, but at a different stage than PRF1. A mutation in *Munc13-4*, which is highly expressed in hematopoietic cells, interferes with cytolytic granule secretion, resulting in a widespread accumulation of lymphocytes, mature macrophages, and sometimes hemophagocytosis (Cincinnati Children's Hospital, 2006). The faulty granule exocytosis resulting from the *Mund13-4* mutation does not negatively impact the polarization of granules or docking with the plasma membranes, but nonetheless interferes with the positive secretory lysosome regulator abilities of the gene.

FHLH4. The most recently identified mutation associated with HLH, 9q21.2-22 of the syntax11 gene, has been linked to FLHL4, and is believed to cause defects in the granule secretory pathway (Rudd et al., 2006). Although poorly understood, it is suggested that mutations in Syntax11, expressed primarily in phagocytes and antigen presenting cells, is involved with faulty vesicle trafficking, leading to FLHL4 disease presentation (Rudd).

Epidemiology

Although HLH affects all ages, the disease is primarily found in children (Fisman, 2000). Lacz et al. (2006) reports that nearly 1.2 million cases of HLH are diagnosed worldwide, each year. More specifically, Fisman cites an annual incidence of 1.2 cases of FHLH per million births in Sweden. Despite the large number of HLH cases that have been diagnosed in northern European countries, statistical proof of this trend has yet to be published due to poor reporting and undiagnosed cases from other areas of the world (Lacz). More distribution data was

collected during investigation of a gene mutation associated with HLH where Rudd et al. (2006), found a particular mutation only in families of Turkish origin. Janko & Stadt (2005) cited a review in which more than half of the HLH cases diagnosed before 1996 were from the Far East. Additionally, HLH appears to be evenly distributed among the sexes (Lacz).

As outlined in Table 2, Rudd et al. (2006) recognizes that the autosomal recessive inheritance pattern of FHLH appears as a result of four possible chromosomal mutations: 9q21.2-22 (FHL1), 10q21 (FHL2), 17q25 (FHL3), and 6q24 (FHL4). Rudd et al. identifies the genes involved with each mutation as follows: FHLH1 – unknown, FHLH2 – perforin gene (PRF1), FHLH3 - *Munc13-4*, and FHLH4 – syntaxin 11 (STX11).

Table 2. Genetics of HLH.

Disease	Chromosomal Mutation	Affected Gene
FHLH1	9q21.2-22	Unknown
FHLH2	10q21	Perforin Gene (PRF1)
FHLH3	17q25	*Munc13-4*
FHLH4	6q24	Syntaxin 11 (STX11)

According to Marcenaro et al. (2006), 30-40% of FHLH cases result due to a mutation in the PRF1 gene, with 25-30% of cases identifying *Munc13-4* as the causative mutation. The syntaxin 11 mutation has very recently been identified, and thus valid statistics have yet to be compiled regarding its prevalence.

Although any type of infection could trigger HLH, Fisman (2000) identifies specific pathogens that more commonly precede HLH. Fisman stresses that the list includes, but is not limited to: leishmania, brucella, rickettsia, malaria, adenovirus, HIV and HIV-related illnesses (ex. pneumococcal disease, histoplasmosis, etc.), Epstein-Barr virus, tuberculosis, parvovirus, and cytomegalovirus. According to Janka and Stadt (2005), in cases where an infectious agent

was identified in children with reactive HLH, the Epstein-Barr virus was the isolated pathogen 74% of the time.

Clinical Presentation

Marcenaro (2006) identifies the following as manifestations of HLH: hyper-inflammatory syndrome, fever, hepato-splenomegaly, cytopenias, hypertriglyceridemia, hypofibrinogenemia, and possible central nervous system alteration such as seizures and encephalopathy. Janka and Stadt (2005) add such findings as lymph-adenopathy, icterus, and bilirubinemia. Lacz et al. (2006) recognizes cutaneous involvement such as a rash, purpuric macules, papules, and morbilliform eruptions in up to 65% of patients presenting with HLH. Outlined in Table 1 by Fisman (2000) are the proposed clinical criteria for diagnosis of HLH submitted by the Histiocyte Society.

Table 1. Clinical signs and laboratory abnormalities associated with HLH.

Clinical sign	% of patients affected
Fever*	60-100
Splenomegaly*	35-100
Hepatomegaly	39-97
Lymphadenopathy	17-52
Rash	3-65
Neurologic signs	7-47
Laboratory abnormality	
Anemia*	89-100
Thrombocytopenia*	82-100
Neutropenia*	58-87
Hypertriglyceridemia*	59-100
Hypofibrinogenemia*	19-85

Laboratory Diagnosis

Janka and Stadt (2005) refer to the symptoms of HLH as "characteristic but non-specific" (p 2). Due to the lack of specificity, initial laboratory testing can only provide a guide or support a diagnosis (not establish one). High triglycerides, increased ferritin, decreased fibrinogen, and elevated bilirubin are all indicative of an HLH diagnosis providing the physical findings correlate (Cho et al, 2005).

Bone Marrow studies may reveal activated macrophages phagocytizing erythrocytes, leukocytes, platelets, and/or precursor cells. Such phagocytizing macrophages provide the foundation for naming HLH.

Due to the hyperimmune stimulatory pathophysiology of HLH, an assay of cellular cytokines would reveal increases in interferon-γ, tumor necrosis factor-α, and other varying cytokines (Fisman, 2005) such as IL-6, IL-8, IL10, and IL-18, along with increased plasma concentrations of sCD25 and sCD95-ligand (Marcenaro, 2006). Additionally, an evaluation of Natural Killer (NK) cell function would show decreased activity in up to 90% of patients (Lacz et al., 2006).

Finally, genetic and chromosomal studies must be performed to determine if the patient is suffering from primary or secondary HLH. A gene mutation associated with the PRF1, *Munc13-4*, or syntax11 gene would be definitive for FHLH. As outlined above, 4 subclasses of FHLH exist, each associated with a separate gene mutation. PCR sequencing of specific coding regions isolated from buccal samples will detect 99% of PRF1 and *Munc13-4* mutations, allowing for diagnosis of FHLH2 and FHLH3 (Cincinnati Children's Hospital, 2006). However, the specific gene region has yet to be identified for the 9q21-3-22 mutation associated with FHLH1, and due to its recent discovery, testing for syntax11, the gene mutated in FHLH4, is still being developed.

Cincinnati Children's Hospital (2006) quotes a one to two month turnaround time for HLH genetic testing, depending on the specific mutation being evaluated. However, recent research has revealed a possible rapid detection method to differentiate between the PRF1 and *Munc13-4* gene mutations. Marcenaro et al. (2006) propose that CD107a, a marker found on activated NK cells, is displayed in lower levels in patients with the *Munc13-4* than in normal patients and patients with a PRF1 mutation. The detection of CD107a can be accomplished

through a staining procedure, thus providing a more rapid screen for FHLH gene mutations than traditional chromosomal studies.

Treatment

HLH requires immediate treatment, with intent to suppress the hyperinflammatory immune response that causes the patient's most life-threatening symptoms (Janka & Stadt, 2005). In the past, the main line of defense against HLH has been a combination of corticosteroids, intravenous immunoglobulin, and VP-16 (Imashuku, 2000). Another suggested line of defense is that the target of therapy should be the pathogen-infected antigen-presenting cells. However, research has emphasized that this course of action is necessary, but not a cure for HLH, except in the case of leishmaniasis, where patients have responded to treatment with Amphotericin B (Janka & Stadt, 2005). For example, the anti-viral medication Acyclovir does not appear of benefit in the treatment of EBV-associated HLH (Fisman, 2000).

Among the most promising treatments, the Histiocyte Society – developed course of chemotherapy/immunotherapy entitled HLH-94 has proven more effective than other options. The chemotherapy regimen recommends etoposide, a chemical toxic to macrophages, in conjunction with dexamethasone or prednisolone (Fisman, 2000). Because dexamethasone more readily crosses the blood-brain barrier, it is believed to provide better protection against CNS involvement often involved with HLH (Imashuku et al., 1999). Etoposide is especially helpful in EBV-associated HLH, due to its inhibitory effect on EBNA synthesis (Janka & Stadt, 2005). Cyclosporin A, used to regulate the release of cytokines, coupled with plasma exchange or exchange transfusion has also been suggested during the early, less advanced stages of the disease (Imashuku).

All of the above treatment options are more likely to provide continued remission in reactive HLH, as opposed to temporary remission in FHLH. Chromosomal mutations in FHLH require drastic treatment options, with allogeneic bone marrow transplantation being the therapy of choice (Fisman, 2000). This course of treatment is also suggested in the unfortunate, but frequent, occurrence of systemic and CNS reactivation in both primary and secondary HLH (Janka & Stadt, 2005).

Prognosis

Without treatment, HLH is almost universally fatal, and studies show that the mean survival rate without any treatment is 2-6 months (Lacz et al., 2006). With treatment, non-EBV-associated pathogen induced HLH has a 60-70% recovery rate, but that rate decreases when the patient is 30 years of age or more (Fisman, 2000). A study completed by the International Registry for Hemophagocytic Lymphohistiocytosis revealed a 66% 5-year survival rate for patients receiving a bone marrow transplant, as opposed to a 10.1% survival rate of those patients on chemotherapy alone (Lacz et al.). The differentiation between acquired and reactive HLH becomes a factor here, as the prognosis for patients with FHLH that do not receive a bone marrow transplant is very poor, while non-FHLH patients treated with the HLH-94 protocol and no transplant have a higher overall survival rate of 55% (Fisman).

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QUIZ 5

1. The gene mutation 10q21 of the PRF1 gene is associated with which form of HLH?

    a. FHLH1
    b. Reactive HLH
    c. FHLH2
    d. None of the above

2. Which of the following pathogens are known to trigger HLH?

    a. Leishmania
    b. Epstein-Barr virus
    c. HIV related illnesses
    d. All of the above
    e. None of the above

3. Which of the following laboratory test results are characteristic of HLH?

    a. Low triglycerides, decreased ferritin, increased fibrinogen, normal bilirubin
    b. High triglycerides, increased ferritin, decreased fibrinogen, elevated bilirubin
    c. Increased glucose, normal thyroid hormone levels, positive DAT
    d. Increased glucose, abnormal thyroid hormone levels, positive DAT

4. Chromosomal mutations resulting in FHLH (any form) are thought to affect which of the following processes?

    a. Bone marrow production of hematopoietic cells
    b. Kidney filtration
    c. Cytolytic capabilities of Natural Killer and Cytotoxic T Lymphocytes
    d. Antibody production by activated B lymphocytes

5. Which of the following is the recommended course of treatment for FHLH?

    a. Bone marrow transplant
    b. Plasma exchange
    c. Acyclovir
    d. There is no treatment option