An Unusual Triad of Hemophagocytic Syndrome, Lymphoma and Tuberculosis in a Non-HIV Patient

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Patient: Female, 58
Final Diagnosis: Hemophagocytic syndrome • lymphoma and tuberculosis in a non-HIV patient
Symptoms: Dizziness • fever
Medication: —
Clinical Procedure: —
Specialty: Critical Care Medicine

Objective: Rare co-existence of disease or patholog
Background: Lymphoma complicated with hemophagocytic syndrome and tuberculosis has been rarely reported. The clinical and radiological presentation of these potentially fatal conditions can be easily confused and there is a potential for misdiagnosis.

Case Report: We present a 58-year-old Hispanic female who was admitted to the hospital with dizziness and fever. Her initial admission diagnosis was severe sepsis secondary to community acquired pneumonia. She was started on intravenous antibiotics. Due to mediastinal lymphadenopathy, lymphoma was considered as a differential diagnosis for which she underwent bronchoscopy and endobronchial ultrasound-guided sampling of her mediastinal lymph nodes. Lymph node aspirate was suggestive of lymphoma. Initial cultures were negative. Her clinical course was complicated with respiratory failure, cytopenia, and rapidly progressive cervical lymphadenopathy. The patient underwent cervical lymph node excision and bone marrow biopsy. The pathology of the lymph nodes confirmed T cell lymphoma, and bone marrow revealed hemophagocytosis. The patient was started on chemotherapy but she continued to deteriorate and died on day 20 of her hospital admission. Post-mortem results of cultures from a cervical lymph node biopsy and PCR were positive for Mycobacterium tuberculosis.

Conclusions: We suggest an aggressive tissue diagnosis with staining for acid-fast bacilli for early diagnosis in patients presenting with hemophagocytic syndrome secondary to lymphoma as coexisting tuberculosis is a consideration. Tuberculosis re-activation should be considered in patients from an endemic region who present with lymphoma and a deteriorating clinical condition.

MeSH Keywords: Lymphohistiocytosis, Hemophagocytic • Lymphoma • Tuberculosis

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**Background**

The presence of lymphoma and tuberculosis in the same patient is not an unusual event. The incidence of tuberculosis in patients with lymphoma has been reported to range from 0.9% to 13.2% and the presence of miliary tuberculosis in malignant lymphoma has been reported to be 35 times higher compared to the general population. Askling and Ekbom reported that the risk of non-Hodgkin lymphoma (NHL) following tuberculosis has been increasing [1].

Hemophagocytic syndrome, also called hemophagocytic lymphohistiocytosis (HLH), is a rare, under recognized hyperinflammatory syndrome. It can be primary (familial) or secondary to several conditions such as hematological malignancies, infections, and inflammatory or autoimmune disorders. Lymphoma is the most common malignancy and Epstein Bar virus (EBV) is the most common infectious etiology implicated in HLH. Infections, including tuberculosis, have been linked to pathogenesis of HLH; it is recommended that once the diagnosis is established, screening for infections such as miliary tuberculosis, EBV, cytomegalovirus (CMV), parvovirus B19, human immunodeficiency virus (HIV), and human herpesvirus 6 (HHV-6) should be considered [2].

HLH is a fatal condition, and it often leads to rapid multi-organ failure. The finding of HLH, lymphoma, and tuberculosis in the same patient is very unusual [3]. We present a case of middle aged female with T-cell lymphoma, HLH, and tuberculosis likely unmasked as a result of fludarabine immunosuppression therapy.

**Case Report**

A 58-year-old Hispanic female with history of hypertension was admitted to the hospital with fever of five days duration and dizziness. She denied dyspnea, cough, chills, night sweats, headache, or gastrointestinal symptoms. There was no history of anorexia or weight loss. She was born in the Dominican Republic and moved to New York City about 20 years ago. She denied use of tobacco, alcohol, or recreational drugs. On examination, the patient was febrile 39.5°C (101.4°F) and hypotensive with blood pressure of 88/40 mm Hg.

Very small, non-tender, soft cervical lymph nodes were palpable. Minimal bilateral rhonchi were heard on chest auscultation. Her abdominal, neurological, and cardiac examination was unremarkable. No organomegaly was found and her skin was intact. Chest radiograph revealed diffuse bilateral infiltrates (Figure 1A). The patient was admitted to the intensive care unit with the impression of severe sepsis secondary to pneumonia. Laboratory parameters were significant for leukopenia (3.2 K/uL), thrombocytopenia (144 K/uL), and elevated serum lactate dehydrogenase (1,142 U/L). Other laboratory results are summarized in Table 1.

The patient received intravenous (IV) fluids, ceftriaxone, and azithromycin for presumptive community acquired pneumonia. She had persistent fever with blood, urine, and respiratory cultures including negative acid-fast bacilli (AFB) stains; her antibiotics were changed to IV piperacillin-tazobactam and IV vancomycin. Transthoracic echocardiogram was normal. Computed tomography (CT) of chest revealed bilateral infiltrates with mediastinal and sub carinal lymphadenopathy (Figure 1B). There was mild splenomegaly noted on CT of
abdomen. The patient underwent flexible fiber optic bronchoscopy (FFB) with bronchoalveolar lavage (BAL), transbronchial biopsies and endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA) on day 6 for high suspicion of malignancy. All cultures from FFB including aerobic, AFB, fungal, and viral, were negative. Pathology from TBNA of the lymph node revealed T cell lymphoma. The following markers were positive: CD4, CD3, CD43, and BCL-2. CD20, CD10, CD79a and PAX5 were negative (Figure 2A, 2B). Tests for T-cell lymphotropic virus-I (HTLV 1) and EBV were not performed.

Her clinical condition continued to deteriorate with development of hypoxic respiratory failure requiring intubation and mechanical ventilation on day 15 of admission. A cervical lymph node excisional biopsy was performed for worsening cervical lymphadenopathy and persistent fever to further evaluate lymphoma. Pathology of the lymph node biopsy was positive for peripheral T-cell lymphoma NOS (not otherwise specified, WHO classification 2008). Immunohistochemical stain results were consistent with T cell lymphoma (NOS) (Figure 3). Additional immunomarkers CD3, CD4, CD5, CD43, and Ki67 >90 were positive; whereas, CD20, CD79A, CD7, and CD15 were negative. A bone marrow biopsy to evaluate pancytopenia revealed hemophagocytic lymphohistiocytosis (Figure 4). Stains of bone marrow for AFB and fungal infection were negative. Patient developed tumor lysis syndrome with acute renal failure requiring hemodialysis and rasburicase. Cyclophosphamide and vincristine for treatment of lymphoma were started on day 19. The patient continued to deteriorate and died on day 20 after admission.

Cultures for AFB from cervical lymph nodes were reported positive for *Mycobacterium tuberculosis* complex identified by direct molecular detection real-time PCR; pathology

### Table 1. Pertinent laboratory parameters.

| Laboratory parameter | Day 1   | Day 7   | Day 15  | Day 17  | Day 19  | Day 20  |
|----------------------|---------|---------|---------|---------|---------|---------|
| WBC (4.8–10.8 k/ul) | 3.2     | 4.3     | 4.4     | 2.5     | 1.5     | 1.5     |
| Hemoglobin (12–16 g/dL) | 13.1    | 12.2    | 11.8    | 9.6     | 8.3     | 8.8     |
| Platelets (150-400 K/ul) | 144     | 129     | 122     | 70      | 37      | 29      |
| BUN (6–20 mg/dL)    | 13      | 11      | 26      | 69      | 64      | 63      |
| Creatinine (0.5–1.5 mg/dL) | 1.2     | 1.0     | 1.5     | 6.1     | 5.2     | 4.8     |
| LDH (110–210 units/L) | 1142    | 3317    | 8677    | 10646   |         |         |
| Ferritin (13–150 mg/mL) | 1844    | >5000   |         |         |         |         |
| Triglycerides (55–150 mg/dL) | 144     | 588     |         |         |         |         |

**Figure 2.** (A) Mediastinal lymph node involved by peripheral T-cell lymphoma. The neoplastic cells are large and anaplastic with cohesive growth pattern (H&E stain, high power). (B) Neoplastic cells strongly positive for CD3. Immunostaining supports the diagnosis of T-cell lymphoma.
stain demonstrated AFB (Figure 5). These results were available postmortem.

Discussion

The presence of lymphoma and tuberculosis in the same patient has been reported in the literature [1,4,5]. Tuberculosis and lymphoma could represent a diagnostic challenge as they share many clinical and radiological features. Fever, night sweats, constitutional symptoms, and weight loss as well as bilateral lung infiltrates and lymphadenopathy can be found in both conditions.

Tissue biopsy remains the most specific and sensitive diagnostic procedure when there is a need to differentiate both conditions. Necrotizing granulomas typical of tuberculosis can be found in both Hodgkin lymphoma [6] and NHL [7]. Therefore, positive cultures for mycobacterium or the presence of acid fast bacilli in a biopsy further analyzed by specific molecular diagnostic testing can be used for confirmatory diagnosis.

In patients from endemic countries, diagnosis of a lymphoma may warrant further work-up to ensure ruling out co-existing tuberculosis. Ruiz-Arguelles et al. concluded that the incidence of tuberculosis in NHL patients is 35 times higher than in the general population [8]. Interleukin 10 (IL-10), which is increased in patients with NHL, has been implicated in the re-activation of tuberculosis [9,10]. The serum concentration of IL-10 has been found to be higher in patients with NHL, which may lead to decreased cell mediated immunity resulting in activation of latent tuberculosis [9]. It has been hypothesized that the risk of NHL is increased in individuals with history of tuberculosis [11,12], though there are studies which found no
association between NHL and tuberculosis [13,14]. There is no experimental data available to support the role of merely latent tuberculosis as an etiological factor for NHL.

HLH is an aggressive and life-threatening syndrome of excessive immune activation which is observed in the children and adults of all ages. The history of this disease dates back to 1939 when Scott and Robb-Smith described it as “histiocytic medullary reticulosis” with features of erythrophagocytosis by proliferating histiocytes. It can be genetic or acquired. The genetic form of HLH is divided into two subgroups depending on whether it is associated with immune deficiencies or not: the familial form has clinical features of HLH only, and the form associated with immune deficiency syndromes has additional distinctive clinical features, e.g., Chediak-Higashi syndrome, Griscelli syndrome, and X-linked proliferative syndrome [15]. Familial forms of HLH were first described in 1952 with consecutive deaths of involved family members [16–18]. The familial forms of HLH usually manifest within the first year of life. HLH is associated with several genetic mutations e.g., PRF1, MUNC13-4, STX1, and STXB2. Since these mutations are inherited in an autosomal recessive manner, there is often a negative family history; they are found in only about 40% of familial cases [19]. The familial forms are diagnosed at an early stage, while secondary HLH can occur at any age. A variety of causes are associated with secondary HLH, including, in order of their prevalence, viral infections, malignancies, rheumatological disorders, and immune deficiency syndromes [20]. The presence of infection was initially thought to differentiate familial forms from acquired forms of HLH; however, it is now clear that most cases of genetic HLH are triggered by infections as well. In secondary HLH, individuals are mostly healthy before the onset of symptoms, while familial forms might be associated with similar prior episodes [21].

Among the infectious causes, virus-associated HLH was first described by Risdall et al. in 1979; most of the described patients were immunocompromised [22]. EBV is the most common viral pathogen linked to HLH and is associated with worse prognosis. Mortality associated with HLH secondary to EBV is even higher if the treatment is not started in a timely fashion [23]. Other viruses commonly described in association with HLH include cytomegalovirus, human herpesvirus 8 (HHV-8), and HIV [24–26]. Since HIV and HLH share several clinical and laboratory features, diagnosis is often delayed in these patients and autopsy studies have confirmed that the condition is underdiagnosed in patients with HIV [27].

HLH associated with tuberculosis has been described in the literature. Brastiano et al. reported a comprehensive literature review [28]. Other infectious organisms, including several bacterial agents, and parasites like leishmanias and malaria, can also have causal association with HLH. Fungal infections e.g., Candida, cryptococcus, Pneumocystis, or Aspergillus cause HLH usually in the setting of AIDS, lymphoma, or other immunosuppressed states [29].

Malignancy is responsible for more than 50% of cases of HLH and hematological malignancies, specifically lymphoma, are the most common cause of malignancy-associated HLH. There is limited evidence as to whether the malignancy itself or increased risk for infections triggers the syndrome in these patients [30]. Patients with autoimmune conditions including systemic lupus erythematosus, connective tissue disorder, dermatomyositis, and systemic sclerosis can develop HLH at any time during the course of disease [31]. A specific term called “macrophage activation syndrome” (MAS) is often applied to HLH occurring in the context of rheumatological diseases. Regardless of etiology, exaggerated inflammatory response and hypersecretion of cytokines also known as “cytokine storm” appears to be the underlying mechanism [32].

HLH constitutes an urgent condition to treat and as its presentation is nonspecific, there is a possibility for it to go unrecognized. Prolonged fever, hepatosplenomegaly, and cytopenia are cardinal symptoms of HLH. Less frequently lymphadenopathy, rash, or neurological symptoms are seen. Characteristic laboratory features include elevated serum triglycerides and ferritin, hyperbilirubinemia with mild to moderate transaminitis, and a low fibrinogen level [33].

The diagnostic criteria initially proposed in 1991 [34] and later updated in 2004 [35] was derived from pediatric patients’ studies only. The diagnosis can be established by identifying a mutation in the HLH gene or if five out of eight criteria are fulfilled; which include fever, splenomegaly, cytopenia affecting at least two of three cell lineages, hyperferritinemia, hypertriglyceridemia, hemophagocytosis in bone marrow, spleen, lymph node or liver, low or absent natural killer cell activity, and increased soluble CD 25 concentration. Many patients fit only two or three criteria and yet have clinical evidence requiring treatment of HLH. Our patient had fever, cytopenia affecting at least two cell lineages, hyperferritinemia, hypertriglyceridemia, hemophagocytosis in bone marrow, and splenomegaly on abdominal imaging. In patients with an established genetic abnormality (e.g., familial hemophagocytic lymphohistiocytosis (FHL) mutation), the diagnosis can be established without meeting the other criteria [21]. In addition, the diagnostic criteria do not apply to macrophage activation syndrome (MAS) because of the overlap of clinical findings between HLH and autoimmune diseases [36]. Moreover, the criteria have been questioned when applied to critically ill patients [37]. Combining these facts with the lack of gold standard tests, makes the diagnosis of HLH an elusive effort even in suspected cases.
Pathophysiological mechanisms for HLH stems from research of primary HLH. The main feature is inappropriate secretion of cytokines by activated cytotoxic T-cells, natural killer cells and macrophages. In patients with T cell lymphoma, cytokines secreted by tumor cells may be a trigger for HLH. Janka et al. postulate that opportunistic infections in immunosuppressed patients may act as a trigger. Either tuberculosis or lymphoma may have acted as trigger [38,39] in our patient.

The prognosis of HLH without prompt treatment is poor. For genetic forms, the median survival is one to two months, and less than 10% probability of survival for three years. Acquired forms of HLH are variable in severity and prognosis, with worse outcomes in malignancy-associated HLH; overall reported mortality for acquired HLH surpasses 50% [33,40].

The treatment of HLH focuses on suppression of hyperinflammatory response, treatment of existing triggers, and in familial cases, correcting defect in immune system. Treatment for genetic and acquired HLH and is aimed at suppression of exaggerated immune response with immunosuppressive agents. Histiocyte Society recommends induction therapy with corticosteroids, etoposide, and cyclosporine for eight weeks [35] and selected cases may need stem cell transplant. However in patients with secondary HLH identifying and treating the trigger seems rational. The role of immunosuppressive therapy is not clear [41].

Our patient represents a very unusual case of HLH presenting as sepsis, later diagnosed as rapidly progressing lymphoma complicated by HLH and M. tuberculosis infection with a dismal outcome. We found only one report in the English literature of these three conditions presenting simultaneously. Ruiz et al. [3] described a 31-year-old female with stage IV high grade NHL who developed fatal HLH, the patient developed miliary tuberculosis after receiving fludarabine. The authors proposed evaluation for tuberculosis and/or consideration of anti-tuberculosis prophylaxis in selected patients treated with chemotherapy. A comparison of our patient with the one described by Ruiz et al. is presented in Table 2.

**Conclusions**

We report this patient case not only for its rarity, but to remind clinicians that the presence of one disease may eclipse another. In patients from endemic countries, diagnosis of a lymphoma may warrant further work-up to ensure ruling out co-existing tuberculosis especially if the patient’s clinical status is deteriorating. In a critically ill patient with an unclear etiology, more extensive testing of tissue, such as AFB and fungal cultures, should be performed. Tuberculosis should be considered as part of the differential in patients with lymphoma when treatment seems to be failing or there are other signs and symptoms that could be considered “atypical” for the condition, like the rapidly growing cervical lymphadenopathy in our patient. HLH is an uncommon and under diagnosed condition with high mortality. It should be considered in critically ill patients if one or two criteria are met and further diagnostic tests, including bone marrow biopsy, should be performed for diagnosis.

**Conflicts of Interest**

The authors have no conflicts of interest to report.

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**Table 2. Comparison of cases.**

| Features                      | Ruiz-Arguelles et al. 2009 | Hashmi et al. 2015 |
|-------------------------------|----------------------------|-------------------|
| Age                           | 31                        | 58                |
| Gender                        | Female                    | Female            |
| Co-morbidities                | Non-Hodgkin lymphoma      | T-cell lymphoma   |
| Fever                         | Yes                       | Yes               |
| Splenomegaly                  | Yes                       | Yes               |
| Cytopenia ≥2 lines            | Yes                       | Yes               |
| Elevated ferritin             | Yes                       | Yes               |
| Thrombocytopenia              | Yes                       | Yes               |
| HLH diagnosis tissue          | Bone marrow               | Bone marrow       |
| Tuberculosis diagnosis tissue | Bone marrow aspirate      | Cervical lymph nodes |
| Immunotherapy                 | Fludarabine               | Steroids and chemotherapy (vincristine and cyclophosphamide) |
| Outcome                       | Death                     | Death             |
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