Case Report

Disseminated *Mycobacterium tuberculosis*: An Unusual Presentation with Associated Hemophagocytic Lymphohistiocytosis

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Hemophagocytic lymphohistiocytosis (HLH) is a rare, potentially fatal, and systemic hyperinflammatory syndrome with exacerbated and uncontrolled activation of histiocytes and lymphocytes against mature cells. Secondary HLH can occur in association with a myriad of underlying infections or malignancies. Our patient is a 38-year-old male prisoner with poorly controlled diabetes and no known other medical conditions. He was referred to our emergency department with three-week history of worsening malaise, weight loss, fever, bruising, and shortness of breath; imaging showed pneumomediastinum, lung nodule, and adrenal mass. Biopsy of the lung nodule revealed acid-fast bacilli. Furthermore, bone marrow biopsy showed foci of necrosis with associated acid-fast bacilli and hemophagocytosis highlighted by CD163 stain; consequently, secondary HLH was suggested. Hence, lab results were reviewed and found to satisfy five of the eight secondary HLH criteria. Moreover, ferritin was >10,000 ng/ml, which has been suggested to be highly suspicious for HLH. He was started on anti-MAC therapy. Unfortunately, the patient’s status declined rapidly; he developed multi-organ failure and succumbed to disease. Later, his culture confirmed *Mycobacterium tuberculosis*. In conclusion, we presented a rare and challenging case of secondary HLH associated with disseminated *Mycobacterium tuberculosis*. A high index of suspicion is required for early diagnosis and treatment, and pathologists should be aware of *Mycobacterium tuberculosis*’ association with secondary HLH.

1. Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a systemic, hyperinflammatory syndrome with uncontrolled activation of histiocytes and lymphocytes against mature cells and their hematopoietic precursors within the reticuloendothelial system [1]. Additionally, there is cytokine overproduction, and consequently, hypercytokinemia (so called “cytokine storm”) can cause end-organ failure and death. It can be misdiagnosed as sepsis, among other entities, given significant clinical and laboratory overlap [2]. HLH is classified into two forms, primary or familial, which is due to a variety of genetic defects, and secondary or acquired, which is associated with a myriad of causes including infections, malignancies, and autoimmune diseases [3]. Although HLH secondary to infection is predominantly viral in origin, especially Epstein–Barr virus (EBV), bacteria such as mycobacteria, fungi, and protozoa can trigger secondary HLH as well [4]. *Mycobacterium tuberculosis* (MTB) has diverse clinical presentations and complications; thus, it can be a great challenge for clinicians to diagnose. It is rarely complicated by HLH [1, 5]. Furthermore, spontaneous pneumomediastinum is a rare presentation of MTB [6]. Despite this, our patient presented with spontaneous pneumomediastinum and developed secondary HLH. Tuberculosis-associated HLH (TB-HLH) has high mortality rate [1, 5], and a high index of suspicion is required by pathologists and clinicians alike to start prompt treatment with anti-tuberculous therapy (ATT) [7]. We report an unusual presentation of disseminated MTB associated with secondary HLH in a patient with uncontrolled diabetes mellitus.
lobe lung nodule.

lobe lung nodule, left adrenal mass, and small

pelvis at an outside facility, which revealed a right lower

computerized tomography (CT) scans of chest, abdomen,
mild splenomegaly and petechial rash involving the ab-

and rash. On day of hospital admission, he was found to have

increasing fatigue, shortness of breath on exertion, weight loss,

and rash. On day of hospital admission, he was found to have

mild splenomegaly and petechial rash involving the ab-
dominal wall and lower extremities, with no other pertinent
positive findings on physical examination. He underwent
computerized tomography (CT) scans of chest, abdomen,
and pelvis at an outside facility, which revealed a right lower
lobe lung nodule, left adrenal mass, and small
pneumomediastinum.

Initial laboratory examination revealed normocytic
anemia, hemoglobin of 8 g/dL, white blood cell (WBC)
count of 9,300/mm^3, platelet count of 76,000/mm^3, absolute
reticulocyte count of 1.7, fibrinogen of 321 mg/dL, pro-
thrombin time /international normalized ratio (PT/INR) of
11.0 seconds, activated partial thromboplastin time
(aPPT) of 26.3 seconds, lactate dehydrogenase (LDH) of
1138 U/L, haptoglobin <30 mg/dL, ferritin of 10,398 ng/mL,
iron saturation of 68%, total iron binding capacity of
137 mcg/dL, total bilirubin of 0.7 mg/dL, aspartate aminotransferase (AST) of 66 U/L, alanine aminotransferase (ALT)
of 57 U/L, and creatinine of 0.54 mg/dL. Bronchoscopy on
hospital day 2 ruled out airway trauma as a cause for
pneumomediastinum. Repeat CT imaging showed increase
in size of right lower lobe lung nodule and stable size of left
adrenal nodule (Figure 1).

Differential diagnosis based on initial presentation
included primary lung malignancy metastatic to adrenal
gland versus malignancy of unknown primary versus in-
fected process. Differential diagnosis for cytopenia in-
cluded anemia of chronic disease secondary to presumed
malignancy, marrow infiltration secondary to metastatic
disease or other marrow infiltrative process, and/or HLH
related to malignancy or infection. On day 7 of admission,
patient underwent CT guided biopsy of the right lower lobe
lung nodule, which revealed numerous acid-fast bacilli
(AFB), without evidence of malignancy. A bone marrow
biopsy performed on day 14 revealed prominent increase in
macrophages with hemophagocytosis within aspirate
smears (Figure 2(a)). The bone marrow biopsy showed
small areas of necrosis (Figure 2(b)). CD163 stain further
highlighted the hemophagocytosis (Figure 2(c)). Acid-fast
microorganisms were noted on FITC stain (Figure 2(d)).
The H Score [8] was utilized, and a score of 195 was ob-
tained, indicating an 80–88% probability of HLH. Hence, a
preliminary diagnosis of disseminated mycobacterial in-
fec tion with secondary HLH was made. Initial suspicion
was for *Mycobacterium avium* complex (MAC), and the
patient was initiated on empiric anti-MAC therapy with
aminocin, rifampin, ethambutol, and azithromycin.
Unfortunately, before HLH directed therapy could be
initiated, the patient had clinical deterioration with multi-
organ failure (acute liver and renal failure), disseminated
intravascular coagulation, and acute hypoxic respiratory
failure requiring mechanical ventilation. The patient’s
clinical condition continued to rapidly deteriorate, and he
subsequently expired on day 18. Posthumously, we re-
ceived results of AFB cultures from bronchoalveolar lavage
indicating MTB infection.

2. Case Description

A 38-year-old incarcerated male patient with a medical
history of newly diagnosed type 2 diabetes mellitus and
tobacco abuse was transferred to our inpatient facility for
further evaluation of spontaneous pneumomediastinum.
Three weeks prior to presentation, the patient noted in-
creasing fatigue, shortness of breath on exertion, weight loss,
and rash. On day of hospital admission, he was found to have
mild splenomegaly and petechial rash involving the ab-
dominal wall and lower extremities, with no other pertinent
positive findings on physical examination. He underwent
computerized tomography (CT) scans of chest, abdomen,
and pelvis at an outside facility, which revealed a right lower
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disease or other marrow infiltrative process, and/or HLH
related to malignancy or infection. On day 7 of admission,
trigger secondary HLH as well [4, 11]. TB-HLH was first reported in 1980s [8]. MTB is an obligate intracellular pathogen that induces TH1-mediated cytoxicity with activation of NK-cells and macrophages resulting in the release of chemokines and cytokines including TNF-α, IFN-γ, IL-1, IL-6, IL-18, and GM-CSF, thus resulting in a cytokine storm [1]. In Per Tseng et al.’s study, 23% of all infection induced HLH was related to MTB. It was also associated with longer duration of symptoms and a higher mortality rate [5]. This was reflected in our patient’s case, as our patient died as a result of TB-HLH.

Most TB-HLH patients present with a fever of unknown origin (FOU), hepatosplenomegaly, and cytopenias [12]. However, to the best of our knowledge, this is the first reported TB-HLH case to present with spontaneous pneumothorax. Our patient had multiple risk factors contributing to the development of TB including a history of type 2 diabetes and incarceration.

TB-HLH has a varied course, with an overall high mortality. Given the rarity of the condition and typical delays in diagnosis, patients with TB-associated HLH tend to have poorer outcomes, with reported mortality ranging from 50% [13] to 100% [1] without treatment. Padhi et al. reported that based on a literature review performed from January 1975 to March 2014, there was 63 cases of TB-HLH with a reported fatality rate of 49% (31 of the 63 patients studied) [1].

Bhattacharyya et al. reported that there may be a delay in diagnosis of HLH for multiple reasons including concordant liver failure and coagulopathy. In our case, our patient developed liver dysfunction and coagulopathy, which may have obscured/delayed the TB-HLH diagnosis [5]. Moreover, there is significant clinical overlap between HLH and septic shock, thus further complicating diagnosis; however, HLH can be diagnosed if there is a mutation in a known causative gene (primary/familial) or if at least five of eight HLH-2004 criteria are met (secondary) as shown in Table 1. Our patient fulfilled total five criteria out of eight as per HLH-2004 protocol including (cytopenias, fever, splenomegaly, hemophagocytosis, and hyperferritinemia). A new scoring system was introduced in 2014 called H Score which helps to avoid under-diagnosis of HLH. It consists of nine variables as shown in Table 2. There is a possible number of points assigned to each variable, and then the H Score is calculated. Our patient had a score of 195, indicating an 80–88% probability of HLH.

Regarding therapy, the goal of treatment in HLH is to curtail the widespread inflammation and multi-organ failure caused by excessive activation of the immune system [15]. This consists of a regimen of immune therapy plus chemotherapy aimed at suppressing the cytokine storm associated with HLH. When a precipitating cause is identified, therapy is aimed at treating the underlying condition such as ATT for patients with TB-HLH, which may be sufficient in cases with mild presentation. Two treatment protocols have...
been developed in the treatment of primary HLH, HLH-94 [7] and HLH-2004 [16], which include agents such as dexamethasone, etoposide, and cyclosporine as backbones of therapy. Patients are initially placed on an induction regimen with these agents. Those who recover are weaned off therapy, while those who do not respond proceed to hematopoietic stem cell transplant. No clear guidelines exist on timing of initiation of immunomodulatory therapy in cases of secondary HLH.

Specifically, in the case of TB-HLH, literature review reveals that patients have been treated with ATT alone or ATT in combination with HLH-specific therapy. Patients who were started on ATT with or without immunotherapy had better outcomes than those who received no treatment at all [13]. Often, treatment with agents such as etoposide and cyclosporine is not feasible due to fulminant multi-organ failure at time of diagnosis, as was seen in our case. This further highlights the need for increased awareness of HLH, with paramount importance given to a search for secondary causes such as TB, as early diagnosis and prompt initiation of treatment could be lifesaving in an otherwise fatal illness.

4. Conclusion

TB-HLH is a life-threatening condition often with delay in diagnosis and a high fatality rate. A high index of suspicion is required by pathologists and clinicians as it may present with unusual findings such as spontaneous pneumomediastinum. Prompt treatment with ATT and potentially HLH-directed therapy may dramatically result in a better outcome.

| Parameter                        | Status                        | Score |
|---------------------------------|-------------------------------|-------|
| Known underlying immunosuppression | No                            | 0     |
|                                 | Yes                           | 18    |
| Organomegaly                    | Hepatomegaly or splenomegaly  | +23   |
|                                 | Hepatomegaly and splenomegaly | +38   |
| Number of cytopenias            | 1 lineage                     | 0     |
|                                 | 2 lineages                    | +24   |
|                                 | 3 lineages                    | +34   |
| Ferritin, ng/mL (or μg/L)       | <2000 = 0                     | 0     |
|                                 | 2000–6000                     | +35   |
|                                 | >6000                         | +50   |
| Triglyceride, mg/dL (mmol/L)    | <132.7 (<1.5)                | 0     |
|                                 | 132.7–354 (1.5–4)             | +44   |
|                                 | >354 (>4)                     | +64   |
| Fibrinogen, mg/dL (g/L)         | >250 (>2.5)                   | 0     |
|                                 | <250 (<2.5)                   | +30   |
| AST, U/L                        | <30                           | 0     |
|                                 | >30                           | +19   |
| Temperature, °F (°C)            | <101.1 (38.4)                 | 0     |
|                                 | 101.1–102.9 (38.4–39.4)       | +33   |
|                                 | >102.9 (>39.4)                | +49   |
| Hemophagocytosis in bone marrow aspirate | No                        | 0     |
|                                 | Yes                           | +35   |

Table 1: HLH 2004 criteria [14].

Table 2: H Score criteria [14].
Conflicts of Interest

The authors declare that they have no conflicts of interest.

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