Klebsiella Pneumonia complicated by Hemophagocytic Lymphohistiocytosis: A rare association

Ankita Kapoor[1], Unnati Bhatia[2], Roopali Goyal Gandhi[1], Carlos Portales Castillo[1], and Suryansh Bajaj[2]

[1]Rochester General Hospital
[2]Maulana Azad Medical College

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Abstract

Hemophagocytic lymphohistiocytosis is a rare condition, characterized by excessive cytokine release and inflammatory response. HLH can be primary or secondary to infections, neoplasm or autoimmune conditions. Management includes immunosuppressive agents. Diagnosis of HLH is difficult in the setting of sepsis. We report a case of Klebsiella pneumonia complicated by HLH.

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Key words: hemophagocytic lymphohistiocytosis, hemophagocytic syndrome, hypercytokinemia, *Klebsiella pneumoniae* , corticosteroids, etoposide, bacterial pneumonia

Key Clinical Message

Severe infections may lead to a state of excess cytokine production resulting in a rare, underdiagnosed condition called Hemophagocytic Lymphohistiocytosis. Early recognition of HLH is important as management is complicated and different from sepsis.

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening condition, characterized by uncontrolled activation of lymphocytes and macrophages, leading to excessive cytokine release and inflammatory response[1,2]. HLH can be either primary (genetic) or secondary to immunologically activating processes such as infections (viral more than bacterial), neoplasm or autoimmune conditions. Management is complicated and might include chemotherapy with immunosuppressive and biological agents or may even require haemopoietic stem cell transplant. Insufficient knowledge of this syndrome can lead to delay in diagnosis and initiating appropriate treatment, thus contributing to poor prognosis.

We herein report the case of a 50-year-old African American man diagnosed with HLH secondary to *Klebsiella pneumonia* infection.

Case

50-year-old African American male with history of alcohol dependence, alcohol withdrawal and alcoholic hepatitis presented to emergency room with high grade fever, shortness of breath, productive purulent cough and hemoptysis. He also had abdominal pain, diarrhea, and back pain. His labs were remarkable for pancytopenia (white blood cell count 1500/mcL, hemoglobin 7.8 g/dL, and platelets 95,000/mcL) and elevated liver enzymes (AST 249, ALT 131). Chest X-Ray was suggestive of pneumonia. He shortly progressed to

respiratory failure and septic shock, requiring intubation, pressor support, and broad-spectrum antibiotics with vancomycin, and piperacillin-tazobactum. Patient was found to have necrotizing/cavitary Klebsiella pneumonia complicated with acute respiratory distress syndrome requiring prone positioning. A day later, platelet count trended down to 2000/mcL and was refractory to platelet transfusions. He also developed acute renal failure secondary to volume overload. At this time, hematology was consulted, and hematology performed bone marrow biopsy (as illustrated in figure 1) which revealed histiocytosis with impressive erythrophagocytosis. Diagnosis for HLH was made as it met 5 of the 8 criteria (fever +pancytopenia + ferritin >500 + triglycerides >250 + hemo-phagocytosis on bone marrow biopsy) invariably related with Klebsiella bacterial infection. He was started on etoposide, and dexamethasone 10 mg twice daily, intravenously. Within few days he also developed febrile neutropenia secondary to chemotherapy and HLH, thereafter antifungal (voriconazole), antiviral, and inhaled gentamicin were also added. Hospital course was further complicated with necrosis of digits and toes bilaterally, following which he had to undergo right below knee, right thumb and index finger amputation. After sometime etoposide was stopped and dexamethasone was tapered. After a total of 10 weeks in the hospital he was discharged home.

Discussion

This was a remarkable case of cavitary pneumonia caused by *Klebsiella pneumoniae* in the setting of recurrent pneumonias by the same organism complicated by HLH. Klebsiella pneumonia is known to be a serious infection and prompts a grim prognosis. Once the organism enters human body, it is notorious to display high degree of virulence and antibiotic resistance[3]. It is considered one of the most common cause of hospital acquired pneumonia in the United States. Host factors that predispose to colonization and infection include intensive care unit admission, immunocompromised individuals, prolonged use of invasive devices, and broad spectrum antibiotics. Prognosis is worst in diabetics, alcoholics, elderly, and immunocompromised. Even with ideal therapy, it carries a mortality risk of 30-50%[4,5].

Hemophagocytic lymphohistiocytosis (HLH) is a rare, life threatening condition characterized by overstimulation of the immune system which leads to systemic inflammation, hypercytokinemia and multi-organ failure[2]. It can be either primary or secondary. Primary HLH typically presents in childhood, and is mainly caused by genetic mutations in cytotoxic activity of natural killer (NK) cells and T-cells. Secondary HLH is mainly triggered by immunologically activating processes such as infection, neoplasm, or autoimmune processes. Viral infections, such as Epstein-Barr virus, cytomegalovirus, herpes virus, and human immunodeficiency virus are known to be associated with secondary HLH. Bacterial infections causing HLH are less common, with the majority related to *Mycobacterium tuberculosis* [6]. To the best of our knowledge, association of HLH and *Klebsiella pneumoniae* is rarely reported in the literature.

Hemophagocytosis is an increasingly accepted endpoint of immune dysregulation in sepsis. Evaluation of HLH in septic patients with pancytopenia is not routine, but should be in differential as delay in diagnosis can be detrimental. The diagnosis is established based on criteria in HLH-2004 trial[7] . Moreover, there could be subsequent delay associated with procuring NK cell activity, soluble IL-2 receptor levels, and bone marrow biopsy thus necessitating concurrent empiric therapy in few cases[8]. In our case, diagnosis for HLH was achieved as he met 5 out of the 8 criteria which included fever, cytopenia, elevated ferritin levels, triglyceridemia, and hemophagocytosis on bone marrow biopsy[9]. NK cell activity and sIL2r are important objective markers, even if not tested, diagnosis can be guided by other parameters which are readily available.

HLH secondary to infection is mostly treated with dexamethasone as per the HLH-2004 study as the severity of the disease process warrants an immunosuppressive therapy. Dexamethasone being the preferred steroid because of its highest CNS penetration. In a systematic review by Hayden et al., treatment was highly variable both between and within the studies. Amongst them, sixteen of the eighteen study groups followed etoposide-based treatment, which was also offered to our patient[10]. It has been shown that early initiation of etoposide, within four weeks of symptoms in pediatric population have higher survival benefit compared to individuals receiving etoposide after 4 weeks[11,12]. Also, in a retrospective study conducted by Arca and colleagues in 162 adults with HLH, a trend towards better outcomes was observed when etoposide was employed (85% vs. 74% survival, p=0.079)[13]. Our patient's immunosuppressive therapy could have

contributed to development of recurrent Klebsiella pneumonia infection, but he did not develop HLH again.

As this is a condition observed more widely in pediatric population, it is imperative that new biomarkers and therapies conducted in children should also be promptly studied in adult population[14]. For example, interferon gamma has shown to be a key mediator in HLH, and a pediatric anti-interferon gamma antibody is currently under phase-1 clinical trial[15]. Another pediatric study is underway using hybrid immunotherapy called the HLH-HIT trial (anti-thymocyte immunoglobulin, dexamethasone, and etoposide). These trials can help inform future studies in adult HLH[15].

Conclusion

In conclusion, Klebsiella pneumonia can be complicated by a variety of inflammatory sequelae, including HLH. It is imperative to note that diagnosis of HLH may be under recognized in the setting of sepsis, and the timeframe required to achieve complete diagnostic testing can be exorbitant in critically ill patients. Treatment in patients with HLH secondary to sepsis should be weighed against the risk of further immunosuppression.

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`HLH Figure 1.pdf` available at https://authorea.com/users/412025/articles/520862-klebsiella-pneumonia-complicated-by-hemophagocytic-lymphohistiocytosis-a-rare-association