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An Uncommon Manifestation of Secondary Hemophagocytic Lymphohistiocytosis (HLH) Precipitated by Candida Auris - A Case Report

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1. Abstract

Hemophagocytic Lymphohistiocytosis (HLH) is a rare but severe systemic inflammatory syndrome, often classified under autoimmune conditions. It is characterised by the excessive activation and proliferation of cytotoxic T cells and histiocytes (macrophages), leading to widespread immune dysregulation. There are two types of HLH one is primary and the other is secondary. Infections caused by virulent organisms are the most common precipitating factor for secondary HLH. While common bacterial and viral agents are well-documented in HLH, fungal infections as a precipitant are relatively less described. Among fungi, an HLH association with Candida auris is infrequent, with only ten documented cases in existing medical literature. We report a case of HLH precipitated by a Candida auris infection.

2. Introduction

Hemophagocytic Lymphohistiocytosis (HLH) is a rare but severe systemic inflammatory syndrome, often classified under autoimmune conditions. It is characterised by the excessive activation and proliferation of cytotoxic T cells and histiocytes (macrophages), leading to widespread immune dysregulation [1]. This hyperactive state triggers a hypercytokinemic response, resulting in significant tissue and organ system damage, culminating in multiorgan dysfunction and failure. HLH is classified as either primary or familial HLH, which is caused by inherited genetic mutations that disrupt the function of cytotoxic T cells and natural killer (NK) cells. Symptoms are often severe and present early in life. Secondary or acquired HLH is caused by diverse triggers such as infection, malignancy, autoimmunity, and immunosuppression [1]. Infections caused by virulent organisms are the most common precipitating factor for secondary HLH. While common bacterial and viral agents are well-documented in HLH, fungal infections as a precipitant are relatively less described. Among fungi, an HLH association with Candida auris is infrequent, with only ten documented cases in existing medical literature. Candida auris is a multidrug-resistant yeast, increasingly recognised for its role in severe nosocomial infections and sepsis, particularly within immunocompromised populations [2]. We report a case of HLH precipitated by a Candida auris infection. Our report aims to contribute to the understanding of the clinical manifestations, diagnostic challenges, and therapeutic approaches associated with HLH.

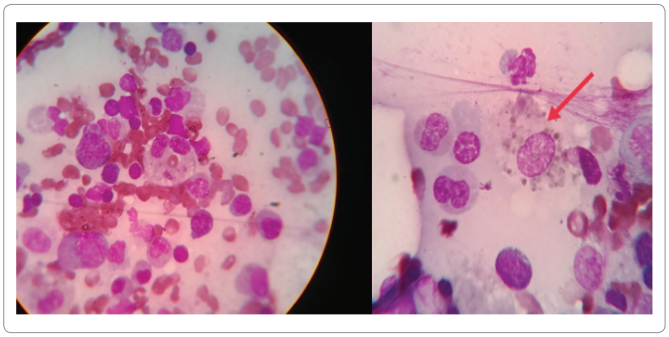
3. Case Report

A 35-year-old female patient to our emergency department with altered sensorium and high-grade fever. The patient was apparently normal 1 month back after which she developed complaints of bilateral lower limb swelling for 1 month which was gradually progressive and not associated with pain. she also had fever for one month which was intermittent and high grade associated with chills and rigours relieved by medication. Over the same period, the patient reported reduced appetite, nausea, and weight loss. She also experienced dyspnea that progressed over the month from New York Heart Association (NYHA) class II to class III. The dyspnea was not accompanied by orthopnea or paroxysmal nocturnal dyspnea (PND). There was no reported history of chest pain, palpitations, or dysuria. The patient is a known case of type 2 diabetes mellitus and has been managed with oral hypoglycemic agents for the past two years. No additional comorbidities were elicited. The patient was treated in another hospital for similar complaints one month back and there was a history of transfusion of two packed red blood cells (PRBC) for anaemia (hb-6g/dl). No other significant family history was present. On examination, the patient was drowsy and not obeying commands, febrile, with a temp of 102.8. Pallor was present and no icterus, cyanosis, clubbing, or lymphadenopathy. Bilateral pitting pedal oedema was noted in both the lower limbs. Her on-arrival vitals were PR- 140 / min (regular), BP-70/40 mmHg, RR-28 /min SPO2- 96% on room air, CBG- 336 mg/dl, Temperature – 102 .8 F Systemic examinationsn was normal CNS-GCS of E3V3M5 (11/15). Local examination revealed Hyperpigmented macules present over bilateral lower limbs with Pus discharge from one lesion located over left ankle region.Patient was shifted to critical care unit and was started on dual inotrope support (noradrenaline and vasopressin)and antibiotics (Inj .Meropenem and clindamycin) 1 unit PRBC was transfused in view of low haemoglobin. As cbg were high and urine ketones were positive patient was started on Inj. Insulin infusion in accordance with the institutional protocol. Emergency incision and drainage of lesion on left ankle region was done and was sent for culture. The patient also had dyselectrolytemia and correction was given appropriately.

During the hospital stay, the patient received targeted antibiotic and antifungal therapy based on urine and blood culture results. Subsequent cultures were obtained, revealing the growth of Candida auris from the central line. Given the lack of significant clinical improvement, a bone marrow biopsy was undertaken. The aspirate revealed a cellular marrow with erythroid hyperplasia and relative myeloid suppression. There were erythro-phagocytosis and platelet phagocytosis features suggestive of HLH. Despite these comprehensive interventions, the patient's condition did not improve significantly, and she ultimately succumbed to the illness.

4. Discussion

Hemophagocytic Lymphohistiocytosis (HLH) is an infrequent but potentially life-threatening disorder. While infections are the primary triggers for secondary HLH, the onset of HLH due to Candida auris, a fungal pathogen, is exceedingly rare, with merely ten cases reported in the literature. This highlights the exceptional nature of the case presented here.Timely recognition, accurate diagnosis, and effective management



of HLH are crucial in preventing substantial morbidity and potential mortality, given the unchecked, pervasive hyperinflammatory response characteristic of this condition. The first prospective international treatment study for HLH, known as HLH-94, established diagnostic criteria based on five key indicators: persistent fever, splenomegaly, cytopenia affecting at least two cell lines (bicytopenia), hypertriglyceridemia and/or hypofibrinogenemia, and evidence of hemophagocytosis [3]. The subsequent HLH-2004 study introduced three additional diagnostic criteria: diminished or absent natural killer (NK) cell activity, elevated serum ferritin levels (hyperferritinemia), and increased levels of soluble interleukin-2 receptors [4]. Collectively, a diagnosis requires fulfillment of any five out of these eight criteria, unless there is supportive evidence from a family history or molecular diagnosis consistent with HLH.Another diagnostic tool is the HScore, wherein each variable is assigned a score ranging from 18 to 64. An HScore exceeding 250 indicates a 99% probability of Hemophagocytic Lymphohistiocytosis (HLH), while a score below 90 suggests a probability of less than 1% [5].It is imperative to consider and recognize HLH at an early stage. The condition often overlaps with other infectious processes, complicating its diagnosis, as numerous infections can manifest with symptoms such as fever, splenomegaly, and elevated ferritin levels. A bone marrow biopsy is crucial for confirming a diagnosis of HLH, as it allows detection of hemophagocytosis and aids in excluding alternative causes of cytopenia.

The primary approach to managing secondary HLH involves addressing the underlying cause while providing robust supportive care. Nonetheless, immunosuppressive therapy is frequently necessary. According to the HLH-94 treatment protocol, dexamethasone serves as the first-line agent for immunosuppression in secondary HLH cases [6]. Should dexamethasone prove insufficient in eliciting the desired response, treatment may require the addition of etoposide and cyclosporine. For selected patients, hematopoietic stem cell transplantation may offer a definitive treatment option for HLH.The mortality rate remains high in patients with HLH. In one case series that included 162 patients, the mortality rate reached 43% with treatment, with a higher mortality rate observed among patients with hematologic malignancy. It is important to note that early diagnosis and prompt treatment are critical in improving the chances of survival for patients with HLH, as the mortality rate can reach 50%-70% if left untreated [5].

5. Conclusion

In conclusion, HLH is an uncommon but potentially fatal disorder marked by an excessively active immune response, often triggered by infections. The unique case of HLH induced by Candida auris underscores the critical need for heightened clinical awareness and a broad diagnostic approach. Early recognition and precise diagnosis are paramount, given the overlapping symptoms with other infectious processes, which can complicate timely identification. Established diagnostic criteria, such as those from the HLH-94 and HLH-2004 studies, along with tools like the HScore, assist in accurately diagnosing this challenging condition.

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