



Case Reports

From EBV-Induced Hemophagocytic Lymphohistiocytosis to COVID-19 triggered Sweet Syndrome: A Polyphasic Clinical Journey

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Abstract

Hemophagocytic Lymphohistiocytosis (HLH) and Sweet Syndrome are two hyperinflammatory conditions, which can be genetic or precipitated by infections, primary immunodeficiencies, autoimmune conditions, or certain therapies and transplants. HLH results because of a exaggerated response by the dysregulated CD+ T cells, leading to widespread activation of macrophages, resulting in hemophagocytosis and excessive, organ-damaging inflammation. Sweet syndrome is another uncommon condition, presenting as sudden onset of painful, edematous, and erythematous papules, plaques, or nodules on the skin, precipitated by the same. It is unusual for them to present sequentially, so herein we present a case of two distinct hyperinflammatory syndromes, Epstein Bar Virus-triggered HLH followed by COVID-19 triggered necrotizing Sweet Syndrome, both occurring in a 53-year-old patient with history of remote history of juvenile idiopathic arthritis within a short time span.

BACKGROUND

Hemophagocytic Lymphohistiocytosis (HLH) is a condition of an overactive immune system, causing widespread inflammation, tissue destruction, and multi-organ dysfunction. Often described as a “cytokine storm,” it can be associated with a genetic defect of lymphocyte cytotoxicity or immune regulation, cancer, underlying rheumatologic disorder, or infection.¹ In HLH, there is ineffective interaction between natural killer (NK) cells, CD8+ cytotoxic T cells, and their targets, which leads to recruitment and activation of cytotoxic cells, which are unfortunately unable to target the pathologic antigen.² This leads to a massive cytokine increase, with activation of macrophages, resulting in hemophagocytosis and excessive inflammation, causing organ damage.²

Sweet syndrome, also known as acute febrile neutrophilic dermatosis, is another uncommon inflammatory disorder characterized by the sudden onset of painful, edematous, and erythematous papules, plaques, or nodules on the skin, which is often accompanied by fever and leukocytosis. The majority of these cases are also precipitated by infections, primary immunodeficiencies, autoimmune conditions and pregnancy. The exact pathogenesis remains unknown, though most theorize that it involves hypersensitivity to bacterial, viral, or tumor anti-

gens that may trigger neutrophil activation and infiltration.³

These inflammatory disorders often have a complex clinical presentation, often resembling infectious etiologies, thereby muddying the diagnosis. This leads to delays in treatment and a poor prognosis. Herein, we present a case capturing two distinct hyperinflammatory syndromes, Epstein-Barr Virus (EBV)-triggered HLH followed by COVID-19-triggered necrotizing Sweet Syndrome, both occurring in the same patient within a short time span. While HLH and Sweet Syndrome individually have been described in rheumatology and infectious disease literature, their sequential occurrence, especially in a patient with resolved autoimmune disease (JIA), is extraordinarily rare.

CASE PRESENTATION

A 53-year-old male has a past medical history of Juvenile Idiopathic Arthritis (JIA), which resolved during his teenage years with prednisone treatment. He presented to the Emergency Department (ED) with a three-week history of night sweats, persistent fevers, fatigue, myalgia, and sore throat. A COVID-19 test performed at home was negative. Physical examination was notable for high fever (104 F), tachycardia, cervical lymphadenopathy, and palpable hepatomegaly. Blood tests showed transaminitis,

hyperferritinemia [14,330 ng/mL (range 11.0 – 307.0 ng/mL)], elevated lactate dehydrogenase (LDH), hypertriglyceridemia, and thrombocytopenia. Inflammatory markers, ESR and CRP, were noted to be mildly elevated. Acute hepatitis panel was negative. Computed Tomography (CT) abdomen revealed hepatosplenomegaly. EBV PCR revealed 50,374 copies with positive IgG and IgM titers. Flow cytometry revealed reactive lymphocytes, but without evidence of lymphoproliferative disorder. The patient received supportive care. However, as he remained febrile, CT of the chest and abdomen was repeated, which showed diffuse hepatic steatosis and rapid interval development of dependent pleural thickening and nodularity, mediastinal lymphadenopathy, and worsening splenomegaly. Liver biopsy was pursued, as he had worsening transaminitis and hyperferritinemia (>16,500 ng/mL), which revealed a non-specific hepatic injury pattern, primarily prominent sinusoidal lymphocytes and macrophages, with equivocal hemophagocytosis. HLH was suspected, thus prompting treatment with intravenous dexamethasone 20 mg daily. His symptoms improved; however, his presentation was thought to be primarily driven by EBV rather than HLH, leading to discontinuation of steroids at discharge.

Two weeks later, he experienced severe right leg pain, presenting to the hospital with fever (104 F), and leg findings suggestive of cellulitis. He was found to be COVID-19 positive, with significantly elevated inflammatory markers. Bullae on the leg raised concern for necrotizing fasciitis, along with blisters in the nose and mouth. He was initiated on IV antibiotics. CT of the right leg showed no abscess or soft-tissue gas, with no evidence of myositis or osteomyelitis. He underwent debridement by the surgical team, and a skin biopsy was performed, which showed a dense neutrophilic infiltrate in the dermis without vasculitis, confirming the diagnosis of the necrotizing variant of Sweet Syndrome. Cultures did not grow any bacteria and remained negative; therefore, antibiotics were stopped. The treatment was then replaced by an intravenous pulse dose of methylprednisolone, with improvement in symptoms. Results for CXCL-9 and IL-2R from the prior hospitalization were elevated: 7535 pg/mL (≤ 647 pg/mL) and 32,525 U/mL (223–710 units/mL), respectively, confirming the diagnosis of HLH. H score was 200. Treatment was continued with high-dose steroids and trimethoprim-sulfamethoxazole for pneumocystis prophylaxis. Anakinra was initiated in an outpatient setting, which has prevented further flares and the resolution of symptoms.

DISCUSSION

In adults, HLH is frequently mistaken for or incorrectly diagnosed as sepsis, primarily because of overlapping clinical features and laboratory results, leading to challenges in prompt diagnosis of HLH.¹ Symptoms typically man-

ifest sequentially, including fever, cytopenias, hepatic or splenic enlargement, transaminitis, hypertriglyceridemia, hypofibrinogenemia, and hyperferritinemia. HLH in adults is primarily characterized by hyperinflammation rather than defective lymphocyte toxicity, and tests evaluating the latter (e.g., flow cytometry for perforin and CD107a) are available only at highly specialized centers.⁴ It is important to differentiate HLH from Macrophage Activating Syndrome (MAS), which is actually a secondary form of HLH caused by underlying autoimmune disease, and for which the treatment is aimed at managing the disease.

In order to diagnose HLH in adults, clinicians must rely on simple, widely available inflammatory markers to differentiate HLH from sepsis and other cytokine-related storms.⁵ Serum ferritin is most closely related to HLH, with a level of more than 3000 μ g/L considered quite sensitive.⁵ Levels of soluble interleukin-2 receptor α (sCD25) of more than 2400 U/mL as measured with functional assays is also very sensitive in adults.⁶ Genetic testing and Natural Killer (NK) cell function tests can also support the diagnosis.¹ Interferon (IFN)- γ -induced chemokines, as CXCL-9, can also help differentiate HLH versus Sepsis.⁷ The patient met 6 of 8 diagnostic criteria for HLH-2004 guidelines⁸: fever for >7 days, splenomegaly, hemophagocytosis on liver biopsy, hypertriglyceridemia, hyperferritinemia, and elevated IL-2R levels. HScore is a tool that can be used to estimate risk of HLH and help decide if further testing is needed.⁹ Our patient had an HScore of 200 points with 80-88% probability of HLH. A significant elevation in IL-2R (>10,000 U/mL) and CXCL-9 helped confirm the diagnosis after malignancies were excluded. The uncontrolled inflammation triggered by EBV and COVID-19 may have contributed to HLH, with the ensuing cytokine storm potentially contributing to the onset of Sweet syndrome in the patient.¹⁰ This necrotizing variant of Sweet Syndrome is rare and aggressive, and will often mimic necrotizing fasciitis, posing a diagnostic challenge. Skin or tissue biopsy is crucial in differentiating infection from inflammatory mimics. The absence of bacterial growth, rapid steroid response, high-grade fever, illness preceded by respiratory infection, and a rapid steroid response strongly supported Sweet Syndrome rather than infection in our patient, per the revised criteria.¹¹ Further, the biopsy results cemented the diagnosis.

This patient initially presented with fever, cytopenias, hepatosplenomegaly, and shock-like features, which resembled sepsis, but in fact were part of EBV-driven HLH. Diagnostic hesitation in distinguishing HLH from infectious etiologies can lead to delays in immunomodulatory treatment.¹² It was evident during initial presentation, where standard infectious workup and empiric antimicrobials failed to yield improvement, whereas immunomodulatory therapy with dexamethasone successfully reversed the clinical trajectory. In addition, the role

of COVID-19 as a potent activator of systemic hyperinflammation has been well-characterized in the context of cytokine release syndrome and HLH.^{12,13} The importance of recognizing immediately and treating appropriately can be emphasized by the fact that for our patient, steroids were mistakenly discontinued after the first admission, and within two weeks, the patient developed Sweet syndrome following COVID-19 infection.

Our patient's presentation reflects a maladaptive form of trained immunity—where a remote autoimmune history (JIA) primes the innate immune system for an exaggerated response upon subsequent viral exposure.¹⁴ 'Trained immunity' enhances the responsiveness and function of innate immune cells upon subsequent stimulation, often providing long-term immune benefits.¹⁵ However, this heightened immune state can become maladaptive, particularly in individuals with a history of autoimmune disease.¹⁵ Patients with remote conditions like JIA may retain subtle immune dysregulation or an 'immune scar'.¹⁵ In such individuals, subsequent stimulation, such as exposure to infectious triggers such as EBV or COVID-19, may provoke an exaggerated and dysregulated inflammatory response, as seen in our case.

CONCLUSION

Hyperinflammatory syndromes, like HLH and Sweet Syndrome, are rare and often are underrecognized, as they are mostly mistaken for sepsis and mismanaged at first. Unexplained, persistent high fever accompanied by hepatosplenomegaly, cytopenias, whether absolute or relative, liver dysfunction, and elevated HLH biomarkers, particularly when unresponsive to antibiotic therapy, should prompt consideration of alternative diagnoses. Without timely recognition and treatment, the condition can progress to multi-organ failure and carries a high risk of mortality. Early identification enables prompt initiation of appropriate immunosuppressive therapy.¹⁶

Disclosures/Conflicts of Interest

The authors have no conflicts of interest to disclose.

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