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Extensive Follicular Crusting with Verrucous Epidermal Hyperplasia and Possible Hemophagocytic Lymphohistiocytosis

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ABSTRACT

A 30-year-old woman, with a medical history including marginal zone lymphoma, systemic lupus erythematosus (SLE), acute pancreatitis, and deep vein thrombosis, presented with extensive facial crusting after chemotherapy and prednisone treatment. Diagnosed with crusted folliculitis, verrucous epidermal hyperplasia, and suspected hemophagocytic lymphohistiocytosis (HLH), this case is unique due to the presence of S. lugdunensis and the complexity of concurrent immunomodulatory conditions and treatments. HLH, a systemic inflammatory disorder, disrupts normal physiological processes, predominantly occurring in childhood but also associated with malignancies and infections in adults.

The patient's presentation involved persistent crusted folliculitis related to S. lugdunensis and a yeast infection. Despite challenges in diagnosis, including concurrent conditions like cytomegalovirus, inflammatory reactions, SLE, and recent malignancy, a bone marrow biopsy confirmed HLH. Elevated ferritin levels prompted consideration of HLH within the broader context of SLE and lymphoma. Treatment with high-dose steroids resulted in improvement.

This case highlights the intricacies of diagnosing complex medical conditions, especially when complicated by the presence of specific pathogens like S. lugdunensis. The identification of this bacterium adds an extra layer of complexity, emphasizing the need for a comprehensive approach to address diverse medical challenges. In immunocompromised patients, a meticulous evaluation is imperative upon HLH diagnosis. The discernment of elevated ferritin levels, coupled with vigilant symptom monitoring, facilitates the

differentiation of HLH from other inflammatory conditions.

BACKGROUND

Hemophagocytic lymphohistiocytosis (HLH) is an acute and rapidly progressing systemic inflammatory condition, characterized by cytopenia, inappropriate cytokine production, and hyperferritinemia.[1] It causes defective apoptosis, through disruption of immune and inflammatory response pathways.[2] Clinically, patients with HLH present with fever, lymphadenopathy, hepatosplenomegaly, multiorgan failure.[1] In addition to the liver and spleen, the lungs, intestines, kidneys, and skin are the most frequently involved organs.[2] In some cases, neurological impairment is observed with poorer prognosis.[2]

The primary form of HLH is seen in early childhood, due to various mutations with genetic inheritance.[1] Mutations in CD8+ T cells and natural killer (NK) cells mutations result in loss of cytolytic pathway proteins such as PRF1, STX11, UNC13D, and UNC18-2.[1] In HLH, the hyperactivation and proliferation of CD8+ T and NK cells results in inappropriate macrophage activation, resulting in phagocytosis of bone marrow hematopoietic cells and/or reticuloendothelial cells. Several cytokines are expressed at increased rates including interferon-gamma (IFN-y), interleukin (IL)-1, IL-6, IL-18, and tumor necrosis factor-alpha (TNFa).[1]

Whereas, secondary HLH is caused by an underlying condition, such as a malignancy, infection, or autoimmune stimulus.[1] Leukemia and lymphoma are the most common types of malignancies which can result in secondary HLH. Infection, particularly with Epstein-Barr virus (EBV) and in some cases members of the Herpesvirus family, HIV, bacteria, and fungi are common triggers.[1]

In a 2019 case report by Thomas et. al. documents a case of HLH arising secondary to SLE in a 22-year-old male.[3] The patient had been suffering with low grade fevers for 3 months prior to it worsening 5 days before admission.[3] Other fever-associated symptoms included altered sensorium, vomiting, facial puffiness, and abdominal distension.[3] Abdominal and pelvic ultrasound yielded hepatosplenomegaly, a common presentation along with HLH.[3] Bone marrow biopsy yielded results consistent with HLH and SLE. Subsequent blood tests revealed elevated ferritin and LDH, and high antinuclear antibody and positive anti double stranded DNA.[3] Following the test, the patient met criteria for HLH diagnosis secondary to SLE.[3] Patient treatment was successful with a combination of steroids and azathioprine.

CASE PRESENTATION

A 30-year-old female, with past medical history of marginal zone lymphoma s/p chemotherapy, systemic lupus erythematosus (SLE) on prednisone, and previous deep vein thrombosis (DVT), presented with extensive facial crusting.

The marginal zone lymphoma was previously treated with four cycles of chemotherapy and discontinued following a DVT. The DVT in the left upper extremity was attributed to port-a-catheter for chemotherapy. The patient was currently taking prednisone, carvedilol, lisinopril, folic acid, enoxaparin SC, allopurinol, and magnesium oxide. The patient's social history was positive for six beers once weekly.

Three months prior to this presentation, the patient was admitted for acute pancreatitis secondary to

heavy alcohol use. Dermatology was consulted at that time for papular eruption, primarily on the face and mid upper chest. That patient reported picking the lesions, but no pruritus. While awaiting the results of the punch biopsy, the patient was started on hydrocortisone 2.5% ointment. The punch biopsy from the chest revealed suppurative folliculitis without evidence of interface or mucin deposition. The patient was then prescribed prednisone 25 mg daily for the management of SLE.

Three weeks after initial discharge, the patient presented for follow up. The lesions on her face had progressed to confluent molds of crusting, with periorbital sparing. A punch biopsy for H&E, PAS, and GMS stains revealed numerous yeast forms within the stratum corneum associated with folliculitis. A pathology consultation noted verrucous hyperplasia with neutrophils and erosive changes on the biopsy. A punch biopsy of deep tissue culture demonstrated 4+ yeast. At this time the patient was prescribed itraconazole 200 mg daily and ketoconazole cream. Patient was advised to continue taking 25 mg for SLE.

Six weeks later, the patient was transferred for treatment of a gastrointestinal bleed on subcutaneous heparin. Dermatology was consulted for progression of facial crusting on itraconazole. Several surface cultures, deep tissue cultures, and punch biopsies were done. The biopsies revealed significant verrucous epidermal hyperplasia, with suppurative folliculitis. A deep tissue culture of the right leg grew staphylococcus lugdunensis and surface cultures from the face grew coagulase negative staphylococcus. Refer to Table 1 to see all Pathology and Microbiology results.

A diagnosis of Crusted folliculitis with verrucous epidermal hyperplasia and possible HLH was made at this time. Warm soaks, urea, benzoyl peroxide, and manual debridement were used to remove the crusting. Bleeding and heme crust developed after debridement, but otherwise it revealed normal epidermis. The patient was started on antibiotics including vancomycin, doxycycline, cephalosporins, trimethoprim-sulfamethoxazole, 120 mg of pulse solumedrol, and hydroxychloroquine. Dapsone was started for PCP prophylaxis with the pulsed steroids.

During her hospital course she was found to have multiple acute and chronic DVTs, a subacute infarct in her left parietal lobe with hemorrhagic transformation, status epilepticus, fevers, and numerous lab abnormalities including anemia, thrombocytopenia, and a rising ferritin value from 1,000 ng/mL to over 7,000 ng/mL. Bone marrow biopsy demonstrated erythrophagocytic histiocytes with significant iron deposition which is concerning for HLH.

The patient's seizures were attributed to her subacute infarct with hemorrhagic transformation. The seizures were controlled with anti-epileptics. Lupus anticoagulants were initially negative, but repeat labs showed a positive dilute russell venom viper test. A diagnosis of HLH or macrophage activation syndrome in the context of SLE was favored given the rising ferritin levels, erythrophagocytosis in the bone marrow, bicytopenia, and fevers. The patient was started on high dose steroids--methylprednisolone 125 mg daily with defervescence of her fevers and improvement in her ferritin level. She was discharged to a rehabilitation institute.

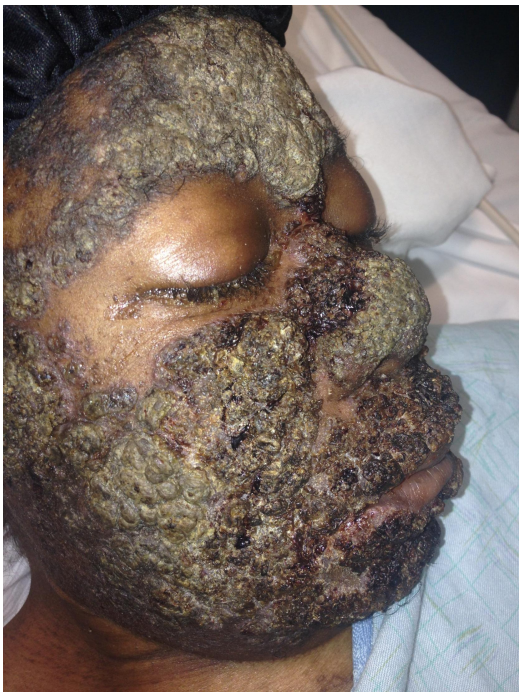

Figure 1: *Extensive Follicular Crusting with Verrucous Epidermal Hyperplasia at First Visit*

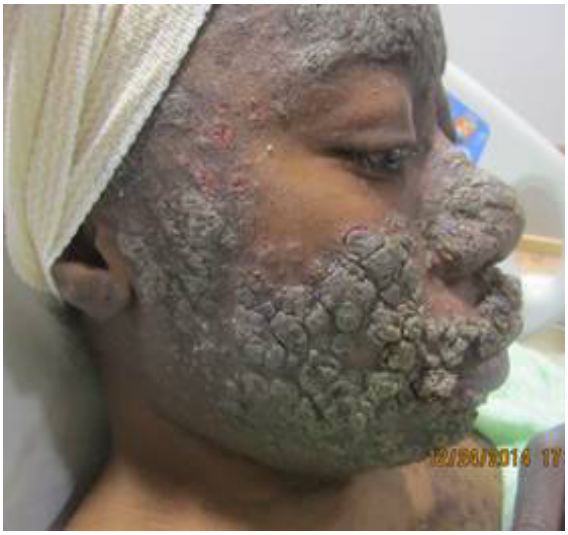

Figure 2: *Extensive Follicular Crusting with Verrucous Epidermal Hyperplasia at Follow-Up Visit*

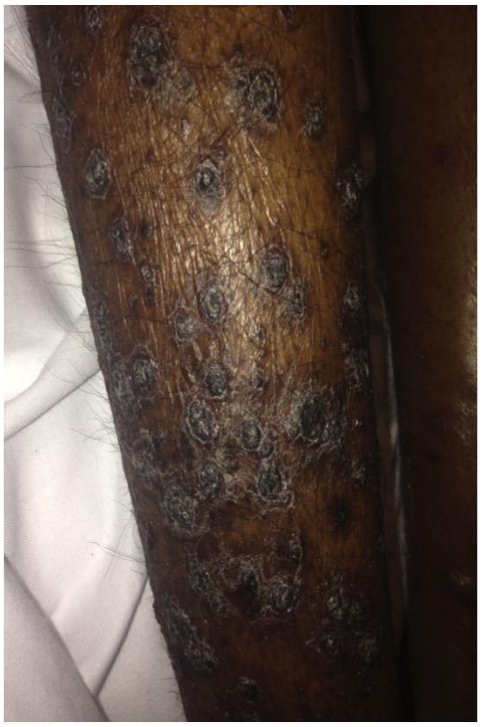

Figure 3: *Crusted Verrucous Lesions on Right Leg at Follow-Up Visit*

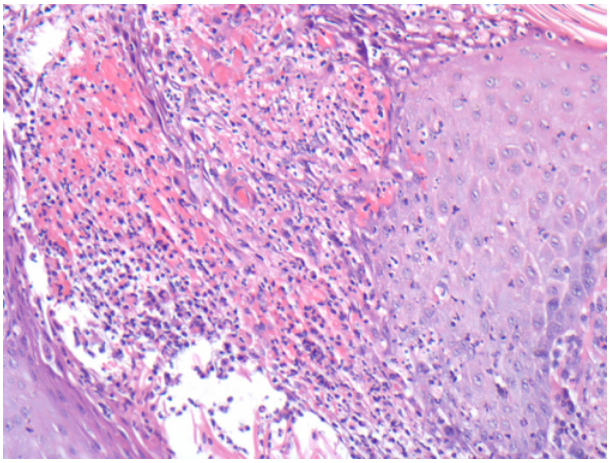

Figure 4: *Punch Biopsy of Left Upper Chest Showing Suppurative Follicululitis with Neutrophilic Inflammatory Infiltrate Distorting the Hair Follicle (H&E 40x)*

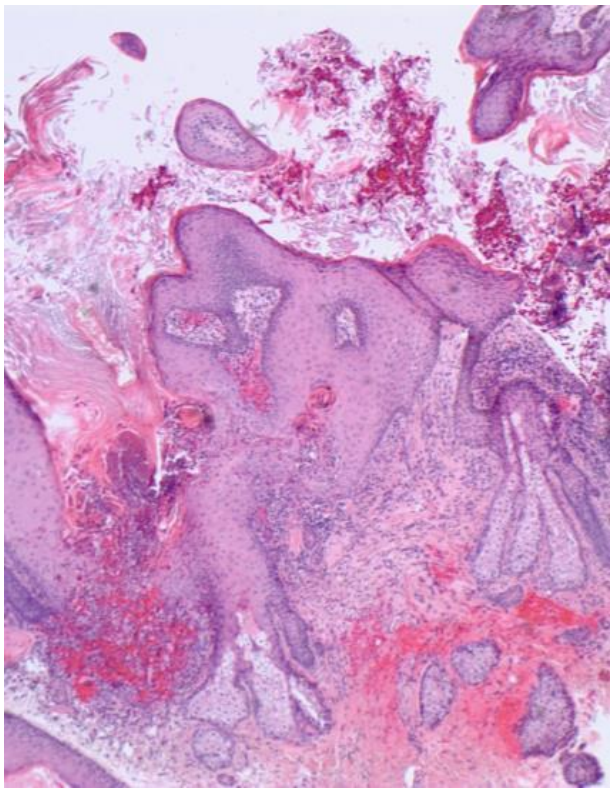

Figure 5: *Pityrosporum folliculitis - Biopsy of Right Jawline with Hyperkeratosis and Suppurative Folliculitis (H&E 40x)*

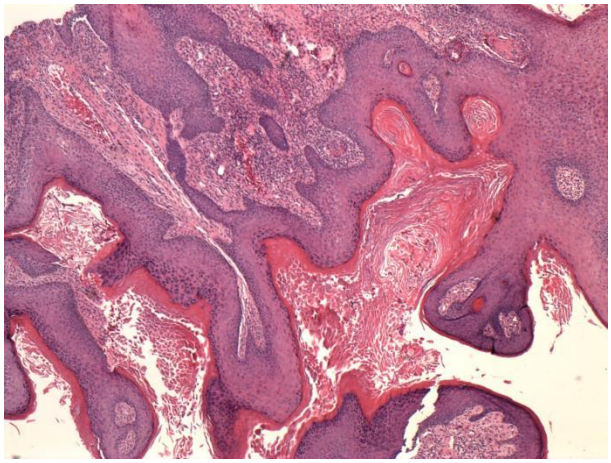

Figure 6: *Punch Biopsy of Lip with Verrucous Epidermal Hyperplasia with both Hyperkeratosis and Parakeratosis (H&E 4x)*

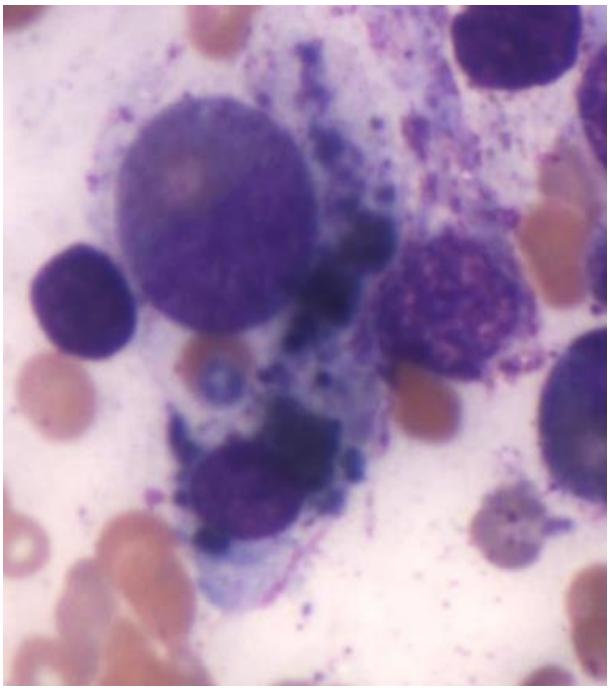

Figure 7: *Possible Hemophagocytic Lymphohistiocytosis in Bone Marrow*

DISCUSSION

This case demonstrates the development of extensive crusted folliculitis involving the face and upper chest in an immunocompromised patient of lupus on treatment with prednisolone and having a past history of chemotherapy-treated marginal zone lymphoma. The sparing of the periorbital area is explained by the decreased size and density of the hair follicles on the eyelids.

A consensus was not reached on a causative organism. The predominant seborrheic distribution of the initial eruption, 4+ yeast on deep tissue culture, lack of bacterial isolates and positive PAS and GMS stains were suggestive of pityrosporum folliculitis. Histopathological examination was suggestive of verrucous epidermal hyperplasia. Cases of pityrosporum folliculitis are known to respond well to systemic antifungal therapy, however the lack of response to 200 mg oral

itraconazole in this case led us to seek alternative explanations for the diagnosis.[4]

The verrucous epidermal hyperplasia led us to consider blastomycosis-like pyoderma (BLP) as a possible diagnosis. BLP, also known as pyoderma vegetans, is caused by a prolonged primary or secondary infection in an immunocompromised patient. BLP is thought to be an exaggerated inflammatory tissue reaction to an infectious agent. It presents as verrucous plaques clinically and pseudoepitheliomatous hyperplasia with microabscesses histologically.[5,6,7] BLP is usually caused by bacteria, most commonly Staphylococcus aureus; however, it has also been reported to be caused by a mixed infection of Staphylococcus epidermidis and Trichophyton rubrum.[8,9] BLP does not respond to antibiotics alone. Systemic retinoids have been used with success.[5]

Deep tissue culture from the leg also revealed a coagulase negative staphylococcus, staphylococcus lugdunensis. The isolation of these organisms in both specimens was not dismissed as commensal growths. Studies have shown that S. lugudensis to be a highly virulent pathogen, capable of causing skin, joint, blood, and endocardial infections. It may behave similarly to staphyloccous aureus and cause nosocomial and community acquired infections. The underreporting of S. lugdenensis in the literature is due to some laboratories not routinely speciating coagulase negative staphylococcus. As the awareness of its pathogenic potential increases and technology for speciation improves, a greater number of cases of S. lugdunensis may be reported in the future.[10,11]

The other organism isolated in our patient, Enterobacter cloacae, is one of the two most commonly isolated pathogens of the genus Enterobacter. It is a part of the normal gut flora and may cause nosocomial infections following the contamination of medical equipment.[12]

The patient also met several of the diagnostic criteria for hemophagocytic lymphohistiocytosis (HLH). HLH can be primary, diagnosed by molecular identification of a characteristic gene mutation or secondary, typically in the setting of a malignancy or infection.[13]

When it is caused by underlying rheumatologic disorder, HLH is referred to as macrophage activation syndrome (MAS). While there is no consensus on the criteria for MAS, but the diagnosis of HLH can be met with five out of eight diagnostic criteria including persistent fever (>38.5 degrees Celsius), splenomegaly, ferritin ≥500 ng/mL, soluble CD25 (IL-2 receptor) ≥2,400 U/ml, low or absent NK-cell activity, cytopenias (≥2 of 3 lineages in the peripheral blood), hypertriglyceridemia (>265 mg/dL) and/or hypofibrinogenemia, and hemophagocytosis in bone marrow, spleen, or lymph nodes.[13,14]

This was a challenging diagnosis as the patient had multiple comorbidities that could have explained some of her lab abnormalities. However, her rising ferritin level was suspicious, particularly in the setting of a low ESR at the time of admission.[13] In a study of pediatric patients with HLH, ferritin values over 3000 were 90% sensitive and 77% specific for HLH; whereas ferritin values over 6000 were 90% sensitive and 90% specific.[15] The etiology for HLH in this case was not clear as she had multiple possible causes including CMV infection, a skin infection with an exaggerated inflammatory tissue reaction, SLE, and a recent malignancy.

CONCLUSION

This case report highlights the challenges associated with the diagnosis of hemophagocytic lymphohistiocytosis, particularly in patients with multiple etiological clues and comorbidities. A

high index of suspicion along with correlation between clinical features, laboratory investigations and histopathological findings is necessary to ensure timely diagnosis and optimize patient management.

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