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A young Saudi female with combined hemophagocytic lympho-histiocytosis and Kikuchi's disease: A case report

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Abstract

Kikuchi's disease is an idiopathic self-limiting condition first reported in Japan in 1972. However, hemophagocytic lympho-histiocytosis is a condition that occurs due to overstimulation of the immune system. The presence of the two conditions is rare, and the clinical observation of this unusual clinical syndrome is worth reporting. We are reporting an 18-year-old Saudi female patient who presented with high-grade fever and diaphoresis 3 weeks before her presentation. Physical examination showed palpable cervical and axillary lymphadenopathy; laboratory investigation found neutropenia, a high lactate dehydrogenase of 550 U/L, and high ferritin levels. A thoracoabdominal computed tomographic study revealed generalized lymphadenopathy. She was diagnosed with hemophagocytic lympho-histiocytosis based on a bone marrow biopsy finding and Kikuchi's disease based on an excisional cervical lymph node biopsy. She received a high dose of dexamethasone with complete resolution of the condition. In conclusion, hemophagocytic lympho-histiocytosis and Kikuchi's Disease are uncommon conditions. The presence of a combination of such two conditions is extremely rare and worth reporting. Early diagnosis and initiation of the management with high dexamethasone dose could save patient life.

Keywords

Hemophagocytic lympho-histiocytosis, Kikuchi's disease, dexamethasone, lymphadenopathy

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Introduction

Kikuchi's disease, or histiocytic necrotizing lymphadenitis, is a benign (non-malignant) disease of the lymph nodes. The main symptoms are swelling of the lymph nodes in the neck, elevated temperature, and diaphoresis. Less common symptoms include weight loss, nausea, vomiting, and sore throat. While the exact cause of this condition is unclear, infectious and autoimmune etiology has been suggested.[1,2] However, hemophagocytic Lympho-histiocytosis (HLH) is an unusual syndrome that can present with fever, jaundice, lymphadenopathy, and splenomegaly, precipitated by infectious or non-infectious causes.[3] We report a case of a young Saudi female patient who presented with fever, weight loss, and lymphadenopathy and was diagnosed as histiocytic necrotizing lymphadenitis with HLH, a rare combination and rarely reported in the literature.

Case report

An 18-year-old Saudi female who is single and with no medical background. On 11 October 2021, she presented to the emergency room with 3 weeks history of documented fever of up to 40°C associated with sweating and

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Table 1. Laboratory results on admission and post-treatment.

Parameters	On diagnosis	Five days after dexamethasone	Reference range
Hematology			
Hgb (g/dL)	10.6	12.0	13–18
WBC (10^3/μL)	2.36	3.63	4–11
Lymphocytes (10^3/μL)	1.6	–	1.5–4
Platelets (10^3/μL)	246	315	150–450
ESR	19		
Chemistry			
Creatinine (μmol/L)	61	60	71–115
BUN (mmol/L)	3.3	3.5	2.5–6.4
LDH (U/L)	550	–	85–227
Ferritin (ng/mL)	356	–	10–219
Serology			
ANA (homogeneous)	1:80	–	Negative
Anti-ds-DNA	Negative	–	Negative
HIV (ELISA)	Negative	–	Negative
CRP (mg/L)	2	1.5	<5

Hgb: hemoglobin; WBC: white blood cell; BUN: blood urea nitrogen; LDH: lactic acid dehydrogenase; AST: aspartate aminotransferase; ANA: antinuclear antibody; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; HIV: human immunodeficiency virus antibody; ELISA: enzyme-linked immunosorbent assay.

painful swelling on the right side of her neck. Her symptoms were associated with poor appetite, and she lost 5 kg. She denied any joint pain, skin rash, or oral ulcer. She had no bleeding tendency or exposure to chemotherapy or radiation. She visited her primary care physician, who prescribed an oral Co-amoxiclav without improvement over 5 days. She was vaccinated for COVID-19 in April 2021 and July 2021 with no complications.

She looked ill and febrile on examination, with a temperature of 38.7 C. Neck examination revealed multiple lymph nodes in the right anterior and posterior triangle varied in size of about 3–4 cm, freely mobile, mildly tender not attached to the deep structures. Otherwise, unremarkable chest, cardiovascular, and abdominal examination, with no palpable splenomegaly or hepatomegaly.

Her initial laboratory workup showed hemoglobin of 13.0 g/dL, a white blood cell (WBC) count was 2.65×10^3/μL, with neutropenia of 0.85×10^3/μL and lymphocyte of 1.60×10^3/μL, lactate dehydrogenase (LDH) of 550 U/L, ferritin 356 ng/mL, and erythrocyte sedimentation rate (ESR) was 19. C-reactive protein (CRP) was 2 mg/L (Table 1). Antinuclear antibody (ANA) was1:80 (homogeneous pattern), and the QuantiFERON test for tuberculosis was negative. Full virology screening, including coronavirus disease 2019 (COVID-19), hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), cytomegalovirus (CMV), and Epstein–Barr virus (EBV) were non-reactive. Peripheral blood film showed leucopenia and neutropenia, and was negative for blast cells. The analysis of triglyceride and interleukin-2 receptor (IL-2R) was not done due to unavailability in our center at that time.

Hospital course

The patient was admitted to the medical ward from the 11th of October 2021 until the 27th of October for a workup; she continued to have fever spikes and poor oral intake. On the second day of admission, bone marrow and lymph node biopsies were performed. After that, she developed an erythematous maculopapular rash in the extensor surfaces of her lower limbs, which was thought to be a reaction related to the perioperative prophylactic Cefuroxime given at the time of the excisional lymph node biopsy. The skin eruption recurred 3 days later, and a punch skin biopsy showed minimal superficial dermal perivascular lymphocytic cell infiltrate consistent with perivascular interface dermatitis, a possible morbilliform drug eruption (Figure 1). Computer tomography of the neck revealed bilateral sub-centimeter cervical lymph nodes; some lymph nodes showed central necrosis (Figure 2). Computer tomography of the abdomen and pelvis showed multiple mildly prominent para-aortic lymph nodes are seen larger one measuring 13 mm × 7 mm, and a few bilateral external iliac nodes are seen, a larger one at 11 mm × 5 mm. Solid abdominal viscera appear grossly unremarkable. Moreover, lymph node histopathology showed partially effaced lymph nodes composed of histiocytes, lymphocytes, scattered eosinophils, karyorrhexis, and apoptotic bodies in a necrotic background with immunohistochemistry diffuse and strongly positive for CD68 (Figure 3).

Bone marrow morphology revealed the presence of hemophagocytes and no blast cells. Active and normal production of the three cell lineages is seen. Limited flow cytometry showed 14% lymphocytes with 70% T cells

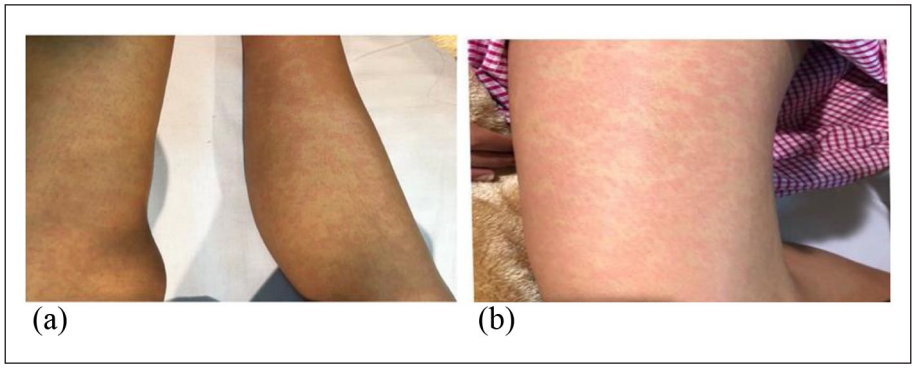

Figure 1. The appearance of an erythematous maculopapular rash in the patient's limbs: (a) bilateral lower limbs and (b) right thigh.

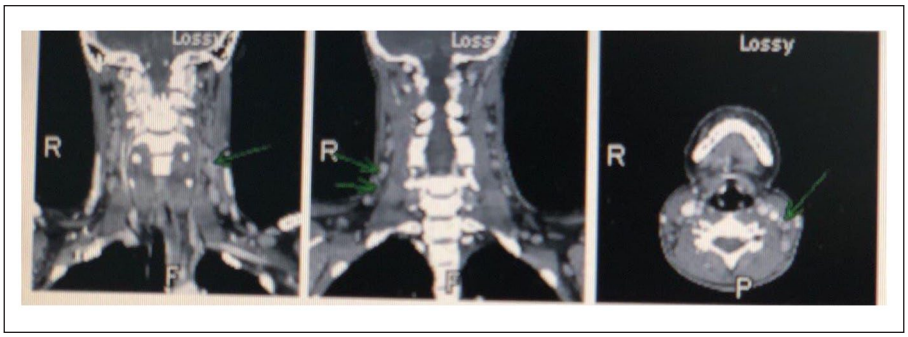

Figure 2. Computer tomography scan of the neck showing bilateral sub-centimeter cervical lymph nodes, some of them showed central necrosis.

(positive CD2, CD3, CD5, CD7, CD8), 25% B cells (CD19), and NK-cell of 5% (CD5–/CD19–) (Figure 4).

Based on investigation results and pathological findings, a multidisciplinary meeting was done, and the patient was started on oral dexamethasone 20 mg P.O. daily for 5 days. The patient dramatically improved, and the fever subsided completely. She regained her appetite; the skin rash did not recur, the size of the cervical lymphadenopathy regressed, and white cell counts rose to near normal.

Discussion

The diagnostic approach is to rule out infectious etiologies, lymphoma, autoimmune disease, and Kikuchi's disease. After a lymph node biopsy is consistent with the diagnosis of Kikuchi's disease and bone marrow biopsy findings, we considered an autoimmune disease as a link between both conditions. The rheumatological workup was inconclusive. This case is considered novel, as it is the first to be reported from Saudi Arabia and had a rare co-existence of the two reported conditions. The clinical utility arises from the challenging presentation of lymphadenopathy and fever that necessitates a workup to rule out underlying malignancies, infections, or autoimmune etiologies. Timely invasive diagnostic modalities may be crucial to reach a diagnosis.

HLH is a rare, life-threatening, systemic inflammatory condition characterized by hyper CD8 activity.[4] Worldwide incidence is unknown but accounts for 1 in 50,000 live births in Sweden. It is either primary HLH so-called Familial type due to genetic mutation, which is presented since birth and inherited as autosomal recessive or secondary (acquired) due to underline infection (in 29% of the cases), immune deficiency syndrome, connective tissue disease or malignancy.[4,5] The overproduction of histiocytes because of immune stimulation by immunogenic triggers leads to the overproduction of cytokines which is the hallmark of disease pathogenesis. As a result, an immune reaction is seen against normal body tissues such as bone marrow, spleen, liver, and lymph nodes.[5] According to the Histiocyte Society criteria to diagnose HLH, we have one or more of the following criteria: (1) presence of a molecular marker that is diagnostic for HLH and (2) presence of four of the following: fever, splenomegaly, cytopenia (either bi-cytopenia or pancytopenia), elevated ferritin, high triglycerides level, low fibrinogen, hemophagocytosis in bone marrow or tissue biopsy, low natural killer cell activity, or high CD25.[5,6] In our case, the diagnosis of HLH was confirmed as she scored four out of nine diagnostic criteria (fever, cytopenia, and high ferritin level, in addition to the presence of hemophagocytosis in the bone marrow biopsy).

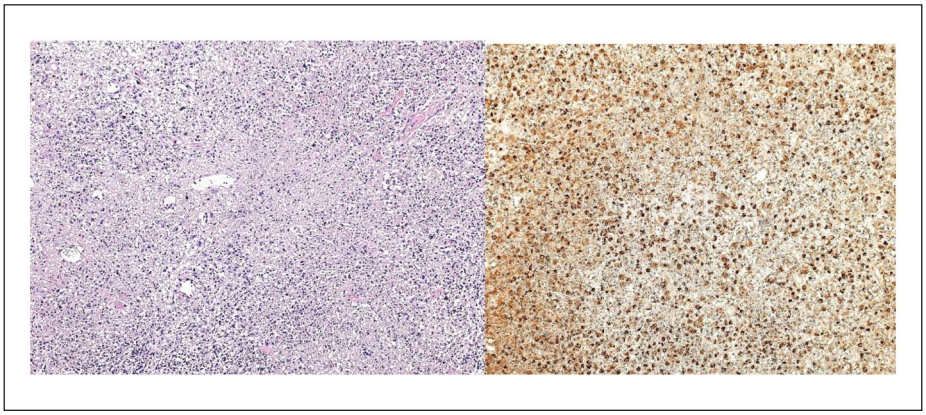

Figure 3. Lymph node histopathology showing histiocytes, lymphocytes, scattered eosinophils, karyorrhexis, and apoptotic bodies in a necrotic background with diffuse and strong positive CD68.

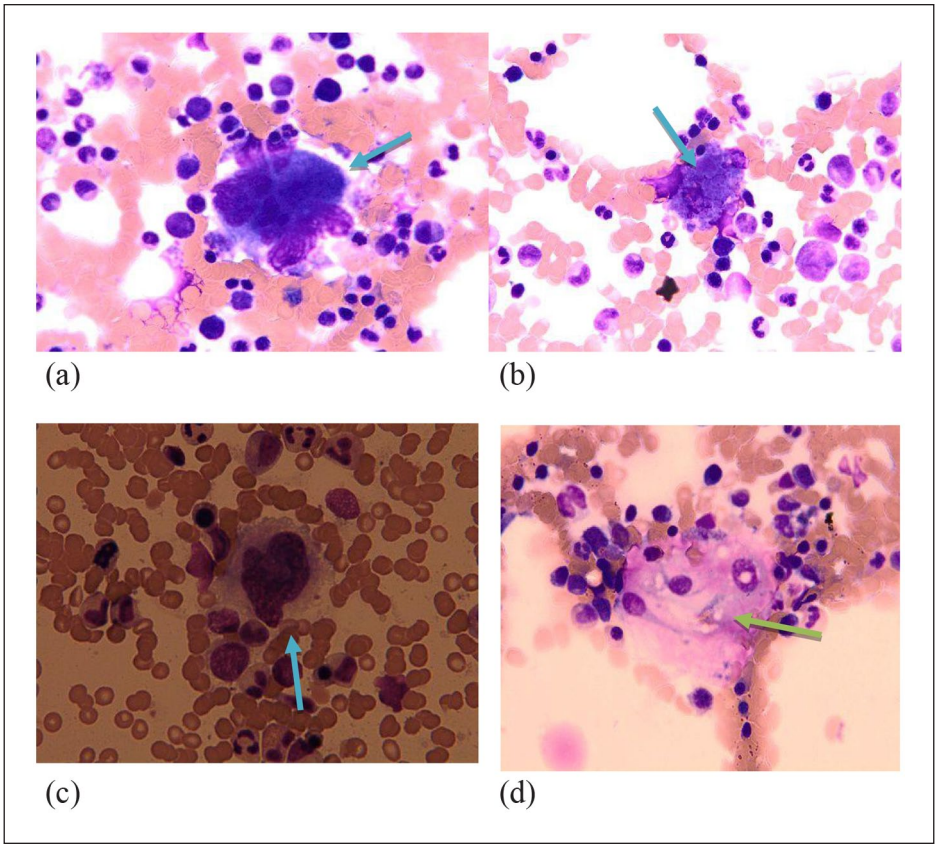

Figure 4. Bone marrow biopsy showing hemophagocyte in the center of the slide with different view (a–c) blue arrows. Histiocytes seen in the mid of the slide (d) green arrow.

Furthermore, HLH affects coagulation in most cases; the condition is characterized by thrombocytopenia, hypofibrinogenemia, and normal factor VIII and V levels. Interestingly, in secondary HLH, the hemophagocytic cell will appear late in the course of the disease, and rarely to find such a cell in bone marrow at first presentation. This clinical fact added value to our case scenario as we had the hemophagocytic cell since admission. However, HLH could resemble macrophage activation syndrome associated with juvenile arthritis, fever, lymphadenopathy, hepatopathy, and cytopenia in the late stages.[7]

The excisional lymph node biopsy was consistent pathologically with Kikuchi's disease, also known as histiocytic necrotizing lymphadenitis, an idiopathic, self-limited

condition; however, proposed etiologies include infectious or autoimmune conditions.[8] Epstein–Barr virus (EBV), cytomegalovirus (CMV), varicella-zoster virus (VZV), influenza virus, parvovirus B19, and human herpesvirus are among the more frequent infectious causes that may be linked to Kikuchi's disease.[9] The reports showed an association between Kikuchi's disease and systemic lupus erythematosus (SLE) in which Kikuchi's disease presented pre, post, or concomitantly to the diagnosis of SLE.[8] Moreover, as the presentation of the disease is almost similar to non-Hodgkin's lymphoma, an excisional lymph node biopsy with positive immunostaining (monoclonal antibody Ki-M1P) helped to differentiate Kikuchi's disease from lymphoma cases.[8,10]

Furthermore, a combination of HLH and Kikuchi's disease was rarely reported. The outcome of Kikuchi's disease alone is much milder than if combined with HLH, which is a potentially fatal condition. Duan et al.[11] reported the case of a 4-year and 5-month-old boy who required aggressive therapy, including corticosteroids, cytochemical agents, and plasma exchange. Nishiwaki et al.[12] reported that a 30-year-old Japanese male with a similar compilation was treated with 1 mg /kg steroid. However, reviewing the literature, high ferritin and high LDH levels indicate the presence of other pathologies, such as HLH, instead of pure classical Kikuchi's disease.[12] Lee et al.[13] reported a 19-year-old Korean male with HLH and Kikuchi's disease who was treated with dexamethasone (10 mg/m^2/day) alone and went to a complete cure within a few days.

An extensive review of the literature showed only 19 cases reported between 2000 and 2016, and only one was reported since then up to the end of 2021. However, most cases were reported in Korea, followed by Japan and Taiwan.[13] Furthermore, around 80% of the cases were treated with corticosteroids with or without an immune suppressive modality, two cases were treated by antibiotic alone, and no one was treated conservatively by NSAID (non-steroidal anti-inflammatory drug). Although Kikuchi's disease is self-limited, HLH is fatal and carries a high mortality rate of up to 70% if not diagnosed and treated as early as possible.[5,14] The treatment modality for HLH includes controlling underlying pathology, corticosteroid (high-dose dexamethasone), chemotherapy as etoposide, and rituximab if the condition is due to EBV. Other modalities such as intravenous immunoglobulin (IVIG), antibiotics, or antivirals may benefit in treating opportunistic infections. In case of no response to a medical modality or in familial (primary) HLH, a bone marrow transplant is required.[14]

A recent relationship between the BNT162b2 mRNA COVID-19 vaccine and the concomitant onset of HLH and Kikuchi's disease has been reported.[15] In that report, the case developed fever, body rash, and lymphadenopathy 3 weeks post the second dose of COVID-19 vaccination. Excessive activity of CD8+ T, which produces systemic inflammatory reactions, could play a vital role in this matter.[15] In our case, post COVID vaccination could be a trigger and valid explanation for the combination of the two pathologies. However, the presentation was more than 3 months post the second dose of the BNT162b2 mRNA COVID-19 vaccine, and she received the third dose after 3 months of her presentation with no further complications or relapsing. We, therefore, hypothesize that there was a delayed systemic inflammatory reaction to the poster dose of BNT162b2 mRNA COVID-19 vaccination.

In our case, the antibiotic therapy of Cefuroxime had led to an adverse reaction secondary to over production of cytokines and histiocytes. However, a high-dose short course of dexamethasone was effective. Our case is unique because it is the first reported case in the kingdom of Saudi Arabia and the second reported case in the Arabian Gulf region after the case that was reported in Qatar in 2007.[13,16] The rationale behind this reporting is to pay attention to the rare disease combination that occurred after a recent COVID-19 vaccination. Early diagnosis and treatment were paramount to a successful outcome in our case.

Conclusion

HLH and Kikuchi's Disease are uncommon conditions; a combination of such two conditions is extremely rare and worth reporting. Early diagnosis and initiation of the management with high dexamethasone dose could save patient life.

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Author contributions

All the authors contributed to the development, writing, and revision of this manuscript. Dr B.G. collected history and laboratory data, Dr R.Y.A.-A. wrote the manuscript and corresponding author, Dr K.A.-Z. contributed to editing and reviewer, and Dr H.W.S is the second reviewer.

Declaration of conflicting interests

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Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

Written informed consent was obtained from the patient for their anonymized information to be published in this article.

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