Epstein-Barr Virus Infection Associated with Kikuchi's Disease and Hemophagocytic Lymphohistiocytosis in Young Omani Female: A Case Report

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Abstract

Kikuchi's disease and hemophagocytic lymphohistiocytosis are rarely seen together and have been rarely reported in the literature. In this case report, we present the case of a 14-year-old female who presented with a two-week history of high-grade fever and neck swelling. Radiological findings showed generalized lymphadenopathy with lung and liver nodules. A biopsy of the lymph node was performed, revealing Epstein-Barr virus associated with Kikuchi's Disease. Patient was started on antibiotics and symptomatic management. However, the patient deteriorated and on further investigation through a bone marrow trephine biopsy, the diagnosis of hemophagocytic lymphohistiocytosis was confirmed and patient was initiated on intravenous immunoglobulin (IVIG) and the Hemophagocytic Lymphohistiocytosis treatment protocol. Notably, the Epstein-Barr virus DNA PCR showed a significant viral load. To the best of our knowledge, this is the first reported case of Epstein-Barr virus infection associated with Kikuchi's disease and hemophagocytic lymphohistiocytosis in Oman.

Keywords: Epstein-Barr virus, Kikuchi's disease, hemophagocytic lymphohistiocytosis

Introduction

Fujimoto disease (KFD), also known as histiocytic necrotizing lymphadenitis, was initially documented in Japan by Kikuchi and Fujimoto simultaneously in 1972. It is typically observed in young women and is rarely found in children and characterized by benign, self-limiting necrotizing lymphadenopathy, which typically resolves within few months.[1,2]

The clinical presentation can vary, but the most common symptoms include fever with painful and/or tender cervical lymphadenopathy. Less common symptoms are weight loss and respiratory and gastrointestinal symptoms.[1-3] Rare presentations, such as skin rash, arthritis, pleural effusion and peripheral and central neuropathy have also been reported.[2] It is important to note that these symptoms are non-specific and can mimic viral infections, autoimmune diseases and even lymphoma. The specific pathogenesis of the disease remains unknown, but it is believed to be triggered by a viral infection or an autoimmune disease.[2,3]

The most consistent laboratory finding in KFD is cytopenia, either pancytopenia or bicytopenia. However, the gold standard method for diagnosing KFD is histological findings of excisional lymph node biopsy, which should be considered alongside the clinical and laboratory findings.[1]

Treatment for KFD is primarily symptomatic and may involve the use of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs). Most patients with KFD have favorable prognosis. However, in rare cases, some patients may experience a relapse or develop an autoimmune disease like Systemic lupus erythematosus (SLE), where in one study; KFD was observed before, after, or at the same time as the diagnosis of SLE.[4]

On the other hand, hemophagocytic lymphohistiocytosis (HLH) syndrome is a life-threatening hematologic disease characterized by the uncontrolled and excessive production of macrophages and histiocytes accompanied by overproduction of cytokines, which is a key factor in the development of the disease.[1,4] Consequently, the immune system attacks healthy tissues such as the bone marrow, spleen, liver and lymph nodes. HLH can be primary or secondary. Primary HLH is a genetic disorder inherited as an autosomal recessive trait while secondary HLH is acquired and can be caused by underlying infections, immune deficiency syndromes, connective tissue diseases or malignancies.[1,2,4]

The Histiocyte Society has established criteria to diagnose HLH, include either the presence of a specific molecular marker of HLH or the presence of at least four of the following criteria: fever, splenomegaly, cytopenia (either bicytopenia or pancytopenia), elevated ferritin levels (500 ng/mL), hypertriglyceridemia, hypofibrinogenemia, evidence of hemophagocytosis in a bone marrow or tissue biopsy, decreased or absent Natural Killer cell activity or elevated levels of soluble interleukin-2 receptor in the serum (sCD25 more than 2,400 U/mL).[4]

The clinical course of HLH varies from complete recovery to rapid deterioration and death.[1]Therefore, the management is more aggressive compared to that required for KFD. The treatment approach for HLH involves controlling the underlying pathology, along with the use of corticosteroids and/or chemotherapy and even intravenous immunoglobulin (IVIG). If the condition is caused by EBV, CD20-targeted monoclonal antibody may also be added to the treatment regimen. In cases where there is no response to medical treatment or in familial (primary) HLH, a bone marrow transplant is necessary.[4]

In this case report, we present the rare association of KFD with HLH caused by Epstein-Barr virus infection in an adolescent female. This association is rarely reported in the literature.

Case Report

The patient was a 14-year-old Omani female with a medical history of chronic tubotympanic suppurative otitis media and hearing loss since the age of five. She presented with two-week history of fever, sore throat and gradually increasing painful neck and jaw swelling, difficulty swallowing and poor oral intake. There were no reported abdominal or urinary symptoms, joint pain or skin rash. Upon clinical examination, the patient exhibited grade IV exudative tonsillitis, oral apthous ulcers and tender bilateral cervical lymphadenopathy without skin changes. Other examinations, including chest, cardiovascular, and abdominal, were unremarkable.

The patient's initial laboratory workup revealed a hemoglobin level of 8.3 g/dL, a white blood cell (WBC) count of 10.3 × 10^9 /µL, neutrophils of 6.82 × 10^3 /µL, lymphocytes of 2.36 × 10^3 /µL, platelets of 640 × 10^3 /µL, and a C-reactive protein (CRP) level of 206 mg/L. The CT scan of the neck with IV contrast was performed on the day of admission and revealed multiple collections in and around the tonsils and the submandibular space. Extensive soft tissue thickening and fat stranding was seen. The lymph nodes exhibited central hypodense areas, indicating the presence of abscesses.

Based on the clinical and radiological findings, a diagnosis of tonsillitis with associated lymphadenopathy was made. The patient was initiated on a course of antibiotics; however, The patient's condition continued to deteriorate, as evidenced by an elevated CRP level of 317 mg/L, a decreased lymphocyte count of 0.55 × 10^3 /µL, and a significant drop in hemoglobin from 8.3 to 6.6 g/dL. To address the low hemoglobin levels, packed red blood cells (PRBC) were transfused on the same day. The blood culture and urine culture yielded no bacterial growth. A throat swab culture revealed normal flora, and the Brucella antibodies test (Abortus and Melitensis) returned negative results. The QuantiFERON test was negative. Antinuclear antibodies were negative with normal complements.

The patient then underwent surgical incision and drainage (I&D) of the pharyngeal abscess. During the operation, left level II and V pathological lymph nodes without abscess were observed. A left submandibular lymph node incisional biopsy was taken for histopathology examination.

The microscopic findings of the lymph node showed a lymph node with effaced architecture and diffuse areas of necrosis without neutrophils, eosinophils and plasma cells, surrounded by immunoblasts and sheets of histiocytes with crescent-like nuclei. Scattered atypical large cells resembling Reed-Sternberg (RS) cells were identified admixed with small lymphocytes, plasma cells, and histiocytes (Figure 1). Immunohistochemistry

revealed that the atypical large cells were positive for CD30, CD20, PAX5 and IRF4/MUM1, but negative for CD15 and ALK. The small background lymphocytes consisted predominantely of CD8+ T-cells with few CD4+ T-cells and B-cells. Numerous histiocytes surrounding the areas of necrosis stained positive for CD68, with focal staining for myloperoxidase were identified (Figure 2). EBV LMP1 & EBER were positive in numerous cells, including small, medium, and the large atypical cells (Figure 3). There was no definitive evidence of lymphoma. The overall findings suggest EBV-associated necrotizing lymphadenitis.

However, the patient's condition worsened. She began experiencing shortness of breath, abdominal distention and watery diarrhea. To assess the situation, a CT scan of the chest, abdomen, and pelvis was performed with IV contrast. The results revealed diffuse lymphadenopathy and significantly enlarged and edematous tonsils, leading to a notable narrowing of the airway. Additionally, lung nodules, pleural effusion, pericardial effusion and ascites were described. Diffuse thickening of colon walls was seen.Ascetic fluid culture showed no bacterial growth.

The patient was then referred to the Royal Hospital for an excision biopsy of the pathological lymph node and for further management. However, the patient's condition worsened, with severe respiratory distress where Noninvasive ventilation (NIV) was initiated. Subsequently the patient was intubated and transferred to the intensive care unit (ICU). Laboratory investigations revealed a further drop in hemoglobin to 6 g/dL, a severe decrease in platelets to 19 x10^3, abnormal coagulation profile, elevated triglycerides, low IgG levels of 3.3 g/dL, but normal IgM and IgA levels. T-cell count was low, with a reverse CD4/CD8 ratio. The immunology team suspected secondary immunodeficiency, most likely hemophagocytic lymphohistiocytosis (HLH). To confirm the diagnosis, a bone marrow trephine biopsy was performed, revealing hypocellular marrow with areas of increased cellularity composed of histiocytes that exhibited phagocytosis of red blood cells. Hematopoietic elements were significantly reduced and small mature lymphocytes were observed in the background. No granulomas were present. Immunohistochemical staining showed CD3-positive mature T-lymphocytes, while CD20 was negative. Increased histiocytes were highlighted by CD68 staining. Focal positivity for Epstein-Barr virus (EBV) was observed within a cluster of large cells. Based on these findings, a diagnosis of marked increase in histiocytes with hemophagocytosis and EBV-positive large cells was made. Further testing with EBV DNA PCR revealed a viral load of more than13x10^ 6 copies, which significantly increased to 213x10^6 copies. With these results, the patient met the criteria for HLH and was initiated on intravenous immunoglobulin (IVIG) and the HLH treatment protocol.
The patient’s blood gases showed severe metabolic acidosis with a high lactate level of 4.8 IU/L, deranged renal failure and anuria. On the final day, the patient's hemoglobin levels continued to decrease, and lactate dehydrogenase significantly rose to 15 mmol/L. The patient exhibited non-reactive pupils and experienced bradycardia and hypotension, despite being on high ventilatory and inotropic support. The patient had cardiac arrest, despite undergoing cardiorespiratory resuscitation (CPR) for over ten minutes; the patient could not be revived from the cardiac asystole and unfortunately passed away.

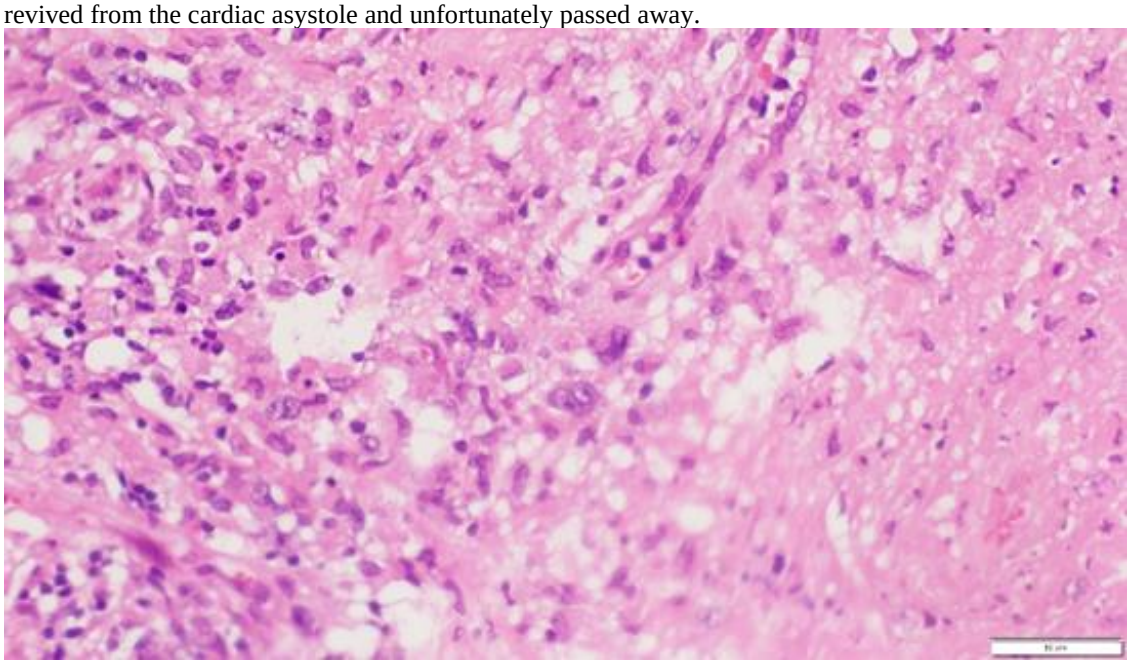

Figure 1: Histocytic infiltrate with large, atypical lymphocyte (center) and area of necrosis with karyorrhexis debris devoid of neutrophils and esinophils (right bottom) (H&E stain, magnification 20x).

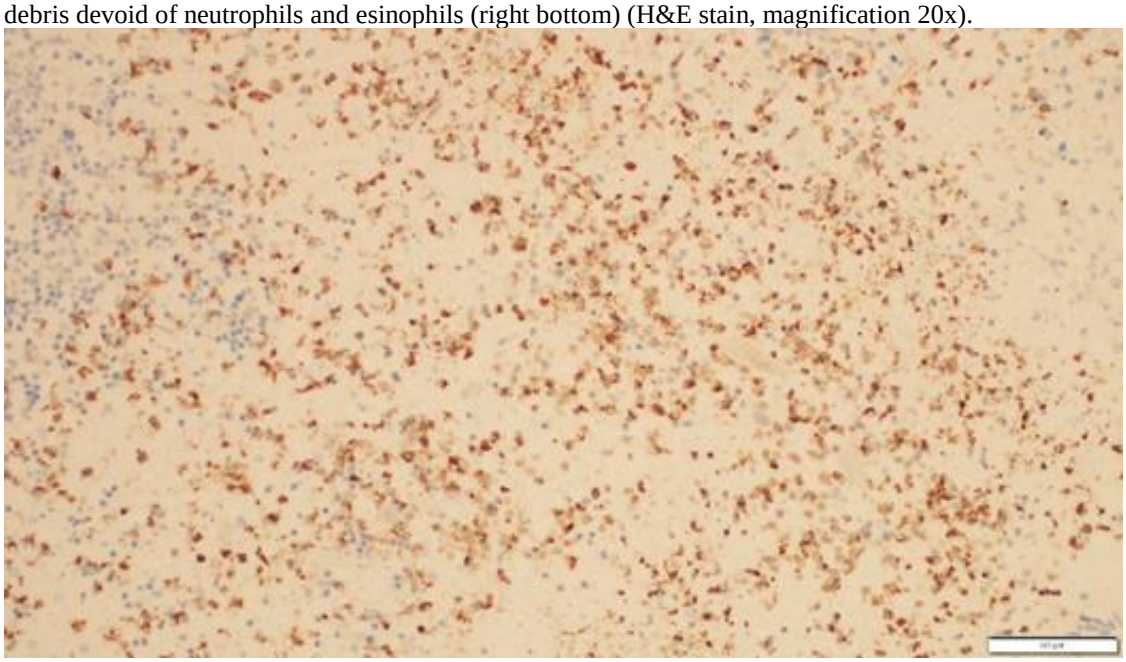

Figure 2: Myloperoxidase IHC staining of histeocytes (magnification 20x).

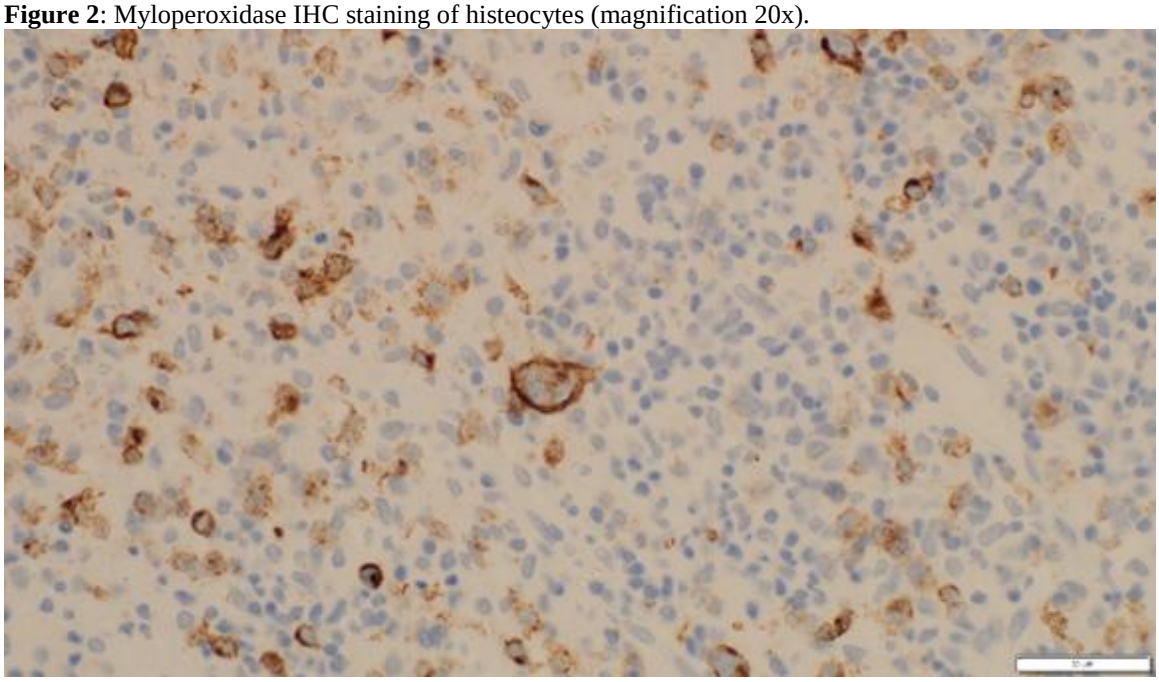

Figure 3: EBV LMP1 immunostain positive in numerous cells including small, medium and large atypical cells (magnification 40x).

Discussion

Kikuchi-Fujimoto disease (KFD) with associated hemophagocytic lymphohistiocytosis (HLH) has been primarily reported in Korea, followed by Japan and Taiwan. Between 2000 and 2023, there have been a total of 20 reported cases worldwide.[4] In the Arabian Gulf, two cases of KFD with secondary HLH have been documented; one in Qatar in 2007 and another in Saudi Arabia in 2023.[4] This case report from Oman is the first known instance of KFD with associated HLH due to Epstein-Barr virus (EBV) infection in the country. In this case, the high load of EBV is belived to be the driven factor that caused both KFD and secondary HLH.

Duan W et al reported that EBV is the most detected virus in secondary HLH, and it has been detected in approximately 74% of the reported cases.[5] However, the literature showed other but less common reported viruses that caused KFD with secondary HLH namely Respiratory Syncytial Virus and parvovirus B19.[5,6]

Lee H-Y et al reported many overlaps in the etiology, clinical symptoms and signs between KFD and HLH. They found lymphadenopathy is the most clinical finding in KFD, but also was the presenting symptom in 68.4% of the cases. On the other hand, fever, splenomegaly and cytopenia were some of the diagnostic criteria for HLH but were also seen in patients with KFD.[1] These findings lead Kelly et al thought that KFD and HLH maybe two stages of a disease continuum rather than a different entities.[7] The histomorphology of the lymph node in our case show complete effacement of architecture due to the expansion of the paracortex. However, partial effacement of the architecture in a background of reactive lymphoid follicles or follicular hyperplasia can also be seen.[1] It was reported that reactive lymphoid follicles and follicular hyperplasia were seen in 60% and 10% of KFD respectively.[8] This was interpreted by some authors as a participation of the B-cell component in the disease process.[8]The expansion of the paracortex is composed of distinct areas of apoptotic necrosis, which contain a large amount of karyorrhectic cell debris devoid of neutrophils, eosinophils and plasma cells as seen in our case and it is a pathognomonic hallmark of KFD.[5,6,9] The absence of neutrophils in the karyorrhexis debris is a key distinguishing factor between KFD Infectious Mononucleosis caused by an acute EBV infection, absent in the former and present in the latter, especially in the context of indistinguishable clinical presentation.[1-3]

SLE with EBV reactivation is another important differential diagnosis as patients with KFD may present with SLE-like clinical features. Both conditions primarily affect young women and it can be extremely challenging, if not impossible, to differentiate between them histologically.[5,7] Turner et al have suggested that the presence of neutrophils and plasma cells is more prominent in association with SLE-associated lymphadenitis, whereas these cells are typically absent or scarce in KFD. Hamatoxyphilic bodies, belived to represent degenerated nuclei that have reacted to antinuclear antibodies, are considered a diagnostic feature of SLE distinguishing it from KFD.[3,5,9] No plasma cells or Hamatoxyphilic bodies within the necrotic areas were seen in this case.

No pathology of the blood vessels in this case was seen although few reported cases of KFD showed thrombosed vessels seen in areas adjacent to the necrotic regions.[5] For instance, vasculitis can also be seen which raise the possibility of autoimmune diseases with vasculitis, commonly SLE, involving the lymph nodes.[5,9]

The extent of necrosis in this case was massive with no residual lymphoid follicles seen. However, the extent of necrosis can vary greatly between cases. Kuo proposed classification of the histopathologic features of KFD into three evolving histologic phases depending on the amount of necrosis: proliferative, necrotizing and xanthomatous. In the early proliferative phase, there is a significant expansion of the paracortex with an increase in various histiocytes, along with a variable number of lymphocytes and karyorrhectic nuclear debris. If any degree of necrosis is observed, the lesion is described as being in the necrotizing phase. If foamy histiocytes are predominantly present within the lesions, regardless of the presence or absence of necrosis, the case is classified as being in the xanthomatous phase.[10]

Another consistent finding in KFD is the presence of crescentric histiocytes, first named by Tsang WY et al, often have a distinctive peripherally located crescent-shape nuclei and voluminous cytoplasm containing esinophilic or karyorrhectic cell debris. Those cells are typically seen at the edge of the necrotic areas.[8] In fact, it has been considered by some authors that the earliest recognizable foci and minimum diagnostic criterion for KFD are paracortical clusters of crescentric histiocytes with karyorrhexis.[9] They express the histiocytes antigens namely CD68 in addition to myeloperoxidase (MPO), CD4, as well as lysozyme.[7,9]

Notably, in our case, there were frequent large reactive but atypical immunoblasts with an appearance resembling Reed-Stenberg cells seen in Hodgkin lymphoma. In our case, the atypical immunoblasts were positive for CD30 and has B-cells immunoprofile (CD20 and PAX5 positive) although the immunoblasts near affected areas in KFD are mostly reported to have T-cytotoxic phenotypes, with a rare B-cell immunoprofile.[2,11]

The presence of atypia in the immunoblasts and their occasional occurrence in clusters and sheets might lead to the diagnosis of high grade lymphoma or Hodgkin lymphoma.[9] However, the presence of the MPO+/CD68+ crescentric histiocytes admixed with atypical immunoblasts favors the diagnosis of KFD in contrast to the MPO negative histiocytes seen in lymphoma. In some situations, distinguishing between those differentials needs specialist input. Menasce et al reviewed a series of 25 KFD cases were referred to their centre, were only 3 cases initially suspected by the referring pathologist to be KFD, while most of the remaining cases were diagnosed, by the refereeing pathologist, as non-Hodgkin lymphoma.[12]

The background of the lymph nodes contains a mixture of small mature lymphocytes and plasmacytoid dendritic cells, the number of each vary between cases. The small mature lymphocytes are predominantly CD8+ T cells, which is in contrast to other types of lymphadenopathy with paracortical T-zone expansion, CD4+ T cells are mainly present.[2,9] This is largely explained by the intense CD8+ T-cell causing apoptosis in the necrotic foci.[9]

Plasmacytoid dendritic cells, on the other hand, are CD4 positive but do not express histiocytic markers or myeloperoxidase.[11] In KFD due to EBV infection, EBV (EBER) staining will be positive in the large transformed lymphocytes (immunoblasts) as well as the background lymphocytes.[4,7]

Conclusion

In conclusion, it is important to highlight that EBV-associated KFD has an excellent poronosis but it can be fatal when secondary HLH occur. Excisional biopsy of the pathological lymph node is necessary to diagnose KFD to narrow down the clinical differential diagnosis and establish a definitive diagnosis which ultimately will lead to an early intervention and improves the survival.

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