

Fever with Twists: A Rare Case of Kikuchi-Fujimoto Disease Complicated by Hemophagocytic Lymphohistiocytosis

Dr. Samreen Shaikh Anwar¹, Dr. Suresh Kanna Subramaniam², Dr. Arvindraj R³, Dr. Gnanaprakash C⁴, Dr. Akita Gopinath⁵, Dr. Aniketh Reddy Gaddam⁶

¹Junior Resident, Department of General Medicine, Sree Balaji Medical College and Hospital, Chennai, India
Email: samreenshaikh120998@gmail.com

²Professor, Department of General Medicine, Sree Balaji Medical College and Hospital, Chennai, India
Email: sureshkannatmc@gmail.com

³Assistant Professor, Department of General Medicine, Sree Balaji Medical College and Hospital, Chennai, India

Email: rarvind2007@gmail.com

⁴Assistant Professor, Department of General Medicine, Sree Balaji Medical College and Hospital, Chennai, India

Email: prakashkmc12@gmail.com

⁵Senior Resident, Department of General Medicine, Sree Balaji Medical College and Hospital, Chennai, India
Email: akitagopinathgopal@gmail.com

⁶Junior Resident, Department of General Medicine, Sree Balaji Medical College and Hospital, Chennai, India
Email: anikethreddygaddam@gmail.com

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Abstract

Background: Kikuchi-Fujimoto Disease (KFD) is a rare, benign, self limiting necrotizing lymphadenopathy, frequently mistaken to be infectious, autoimmune or neoplastic disease. HLH is life-threatening hyperinflammatory syndrome that is capable of sometimes complicating KFD.

Case Presentation: On this occasion, we present a case of an 18-year-old female client who has a history of fever, cytopenias, and neurological symptoms. Primary tests showed the presence of lymphadenitis in keeping with KFD, positive auto-immune antibodies and an increase in inflammatory parameters. She acquired the symptoms of HLH with hyperferritinemia (>50,000 ng/mL), intractable cytopenias, and dysfunction in the organs despite therapy. She needed to be under high-dose corticosteroid therapy, etoposide, intravenous immunoglobulin, and immunosuppressants. Primary HLH was eliminated by genetic testing. The patient improved slowly and was afebrile on follow up, but she went on to have hydroxychloroquine-related retinal toxicity.

Conclusion: The present case demonstrates the possibility of diagnostic difficulty of prolonged fever in young adults and reminds us of the importance of the early detection of HLH in the context of KFD. Timely immunosuppressive treatment and multidisciplinary approach is important to achieve positive results.

Keywords: Kikuchi-Fujimoto Disease, Hemophagocytic Lymphohistiocytosis, Fever of Unknown Origin, Autoimmunity, Case Report

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Introduction

Prolonged fever among young adults is a complex diagnostic issue that is common and may necessitate a thorough and methodical assessment process because of the broad variety of possible causes. Although infectious diseases are the most common cause especially in endemic and resource-restricted settings, a sub-group of patients still displays persistent or recurrent fever despite receiving proper antimicrobial treatment. Autoimmune disorders, inflammatory

conditions and hematological diseases should be put into consideration in these cases. Kikuchi Fujimoto disease (KFD), or histiocytic necrotizing lymphadenitis, is a rather unusual and poorly identified cause of fever of unknown etiology that is mostly associated with adolescents and young women. Clinically, KFD is also similar and is characterized by fever, lymphadenopathy which is mostly cervical, leukopenia and increased inflammatory markers. Despite the fact that the disease is typically non-

Fever with Twists: A Rare Case of Kikuchi-Fujimoto Disease Complicated by Hemophagocytic Lymphohistiocytosis

infectious and self-limiting, the disease is often confused with systemic Lupus erythematosus (SLE), lymphoma, and infectious lymphadenitis, which is why there is a tendency to be confused in diagnosing it. This may also be complicated by the presence of positive autoimmune markers, cytopenias, and systemic symptoms that will usually lead to delayed histopathological confirmations and improper treatment. Pathogenesis of KFD is yet to be fully comprehended but immune disregard, viral stimulants and autoimmune processes have been put forward with the support of the known relationship between KFD and autoimmune diseases, especially SLE.

In uncommon cases, Kikuchi-Fujimoto disease can be complicated by secondary hemophagocytic lymphohistiocytosis (HLH) which is a hyperinflammatory syndrome that is severe and potentially fatal when uncontrolled macrophage and cytotoxic lymphocyte activation occurs. HLH is typified by incessant high-level fever, cytopenias, hyperseronaemia, hepatic dysfunction, coagulopathy, and multi-organic involvement, and its prognosis is high unless it is managed in time. The clinical manifestations of HLH can be confused with the state of severe infection or autoimmune exacerbation, which leads to the further delay in diagnosis, in particular, in the case when it is developed in the background of an already rare disease like KFD. This shift to what is usually a self-limiting disease and to one that is swift in progression and life-threatening indicates the value of being vigilant and at an early stage. The timely administration of immunosuppressive therapy using established guidelines on the treatment of HLH, as well as multidisciplinary management, would be crucial in enhancing the outcome of patients. Since HLH presentation in KFD is rare and few cases have been documented, better documentation of such cases is necessary to increase clinical awareness and direct appropriate diagnosis. Here, we present the case of an adolescent girl with biopsy-confirmed Kikuchi-Fujimoto disease who developed secondary hemophagocytic lymphohistiocytosis and discuss the issues that have been encountered in the diagnosis and treatment of this rare but severe association.

Case Report

A 15-day history of high-grade intermittent fever that is accompanied by chills and headache was histories presented by an 18-year-old Chennai-based college student. No previous history of rash, abdominal pain, urinary, and weight loss. Her history was of febrile

seizures during her early years and had just returned to Ooty where she was exposed to rainfall and trekking.

Clinical findings

She was an afebrile and hemodynamically stable patient on admission. It was found to have generalized erythematous rash and mild splenomegaly. Neurological examination revealed no impairment, but with short-term twitching.

Investigations

The initial workup revealed the presence of leukopenia and thrombocytopenia (CBC: Hb 10.4 g/dL, TLC 3930/mL, platelets 93,000/ml). CRP was elevated, liver enzymes slightly abnormal, LDH greatly abnormal (958 U/L). Negative viral serologies, malaria, and Widal. MRI pelvis showed a benign left ovarian cystic lesion.

ANA was positive (speckled pattern) showing anti-RNP/Sm, anti-Ro52 of the serum, low C3, and significantly increased ESR (127 mm/hr) and ferritin (2967 ng/mL).

Cervical lymph node biopsy revealed necrotizing lymphadenitis that is in line with the Kikuchi-Fujimoto Disease. Bone marrow biopsy showed bone marrow of a hypercellular type with a topography of elevated histiocytes, and no signs of malignancy.

Clinical course

Although corticosteroids were initiated, the patient had the development of worsening cytopenias, seizures, hypotension, and hyperferritinemia (>50,000 ng/mL) which met the HLH-2004 diagnostic criteria. She had to be hospitalized in the ICU, and she was prescribed high-dose corticosteroids, etoposide, IVIG, cyclosporine, and hydroxychloroquine. She needed several blood and platelet transfusion. Some of the complications were pericardial effusion, bilateral pleural effusions, pulmonary edema and clear recurrent mucosal bleeding. Next-Generation sequencing (Genetic testing) showed no known HLH mutations, which favours secondary HLH.

Outcome

In a few weeks, the fever had disappeared, cytopenias had gone, and the inflammatory processes were brought under control. She was healed on tapering doses of the dexamethasone, cyclosporine, and hydroxychloroquine. She still had afebrile on follow up but acquired chorioretinal atrophy caused by hydroxychloroquine.

Discussion

The case has underscored the uncommon but potentially fatal Kikuchi-Fujimoto disease (KFD) and secondary hemophagocytic lymphohistiocytosis

Fever with Twists: A Rare Case of Kikuchi-Fujimoto Disease Complicated by Hemophagocytic Lymphohistiocytosis

(HLH) to involve increased clinical care. KFD is considered to be a benign, self-limiting condition, and mostly it affects young women and either improves with supportive therapy or short-course corticosteroids. Nevertheless, its clinical manifestation is often similar to autoimmune disorders, including systemic lupus erythematosus (SLE) and hematological malignancies, which creates confusion in diagnosing it. KFD can in exceptional cases be the cause of intense immune homeostasis leading to the progression of secondary HLH. This change is a life-threatening shift in disease process, which is usually characterized by a mild nature to an acute exacerbation with a high mortality risk unless it is identified and addressed in a timely manner. HLH is a hyperinflammatory condition caused by the uncontrolled action of macrophages and cytotoxic T lymphocytes, which causes excessive secretion of cytokines and general tissue destruction. It has a clinical presentation that is characterized by protracted high-grade fever, cytopenias, hepatosplenomegaly, liver dysfunction, coagulopathy, and significantly elevated serum ferritin. Extreme hyperferritinemia is an invalid but significant diagnostic feature and may be used to distinguish HLH and uncomplicated KFD or autoimmune exacerbation. In the current case, progressive cytopenias, neurological involvement, dysfunction of organs and a ferritin level of more than 50,000 ng/mL met the HLH-2004 diagnostic criteria, which underlines the relevance of serial clinical and laboratory follow-ups in the patient KFD with no other improvements or clinical deterioration despite initial treatment.

The early diagnosis and early commencement of immunosuppressive treatment is the key determinant of outcome in HLH. High dose corticosteroids, etoposide, cyclosporine, and intravenous immunoglobulin are still the mainstay in the treatment of secondary HLH using HLH-94 and HLH-2004 protocols. Multi-organ involvement and life-threatening complications made our patient need aggressive immunosuppressive therapy and intensive supportive care, but he showed a gradual clinical and hematological progress, which can remind us of the possibilities of positive results when the condition is treated in time and properly.

This patient presents a positive combination of markers of autoimmune disease, which is in favor of the previous insights that have indicated an immunological continuum between KFD and SLE, and HLH. ANA positivity and hypocomplementemia can be transient immune activation instead of an autoimmune disease, although, longitudinal follow-up is necessary, because

some patients who develop KFD later acquire SLE. The case demonstrates the significance of considering HLH as a rare yet dangerous complication of KFD and justifies the necessity of multidisciplinary care and long-term monitoring in patients with this disease.

Conclusion

Kikuchi Fujimoto disease is traditionally said to be benign and self-restricting, but sometimes it is complicated by secondary hemophagocytic lymphohistiocytosis which leads to the severe impairment of the immune system and life-threatening multiple organ involvement. This case highlights the relevance of keeping a high index of suspicion toward HLH in patients with young children that manifest the disease with a long history of fever, cytopenias, and worsening despite the proper initial treatment. Timely histopathological diagnosis, intensive observation of inflammatory indicators, especially serum ferritin, and timely the use of immunosuppressive therapy according to the recommendations of the HLH are essential to ensure the patient has an improved prognosis. The autoimmune serological markers also underscore the complicated immunological interactions between KFD, HLH, and systemic autoimmune diseases and that should be followed up over time to allow the possibility of autoimmune progression. The use of multidisciplinary management and early intervention were central in getting a positive result in this patient and there is a need to ensure that clinicians are aware of this uncommon yet severe association.

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Fever with Twists: A Rare Case of Kikuchi-Fujimoto Disease Complicated by Hemophagocytic Lymphohistiocytosis

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