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Kikuchi Fujimoto Disease: A case report

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Abstract

Kikuchi Fujimoto Disease (KFD) is a rare clinical syndrome. Classically, KFD presents with fever and cervical lymphadenopathy. In most cases, it is a benign self limiting syndrome lasting around one to four months. It has been documented in all ethnic groups but is more prevalent in the Asian population. The diagnosis of KFD can be difficult as its clinical features can be similar to malignant lymphoma and Systemic Lupus Erythematosus (SLE) associated lymphadenitis. A strong association with SLE and sometimes other autoimmune diseases has been noted. Severe extranodal involvement can occur very rarely. A case of severe KFD presenting with features similar to secondary sepsis is unusual. In this report, we discuss a case of atypical Kikuchi's disease which presents with generalized serositis mimicking sepsis. Severe KFD has been known to resolve with corticosteroid administration. Patients with severe disease may need long term monitoring for development of autoimmune disorders.

Keywords

Kikuchi Fujimoto Disease (KFD); lymphadenopathy; sepsis

Abbreviations

KFD: Kikuchi Fujimoto Disease; SLE: Systemic Lupus Erythematosus; ESR: Erythrocyte Sedimentation Rate; INR: International Normalized Ratio; HIV: Human Immunodeficiency Virus; HCV: Hepatitis C Virus; ADA: Adenosine Deaminase; FNAC: Fine Needle Aspiration Cytology; AFB: Acid Fast bacilli; ANA: Anti-nuclear Antibody; ANCA: Anti-neutrophil Cytoplasmic Antibodies; CD: Cluster of Differentiation; FDG-PET: Fluorodeoxyglucose Positron Emission Tomography

Introduction

Kikuchi Fujimoto disease (KFD) is a rare benign self limiting syndrome, classically described as cervical lymphadenopathy with low grade fever. At times, it presents with extranodal involvement which can even be life threatening. Varied presentations have been reported, emphasizing the need for accurate diagnosis and treatment [1-4]. This report aims to discuss a case of atypical Kikuchi's disease which presented with generalized serositis mimicking sepsis.

Case Presentation

A 40 year old male presented with low grade fever for one week followed by abdominal distension

and pain along with vomiting and breathlessness two days prior to admission. He also had bilateral neck swellings for the past one month. He was admitted elsewhere for his complaints and the investigations showed leucopenia, thrombocytopenia, minimally elevated liver enzymes and positive Dengue IgM antibody. Based on these investigations he was treated for dengue fever and also underwent cervical lymphnode excision biopsy. As he worsened clinically with the development of abdominal pain, vomiting and breathlessness he was referred to our center.

On examination he was febrile, tachycardic (PR- 140/min), normotensive (BP- 120/70 mm Hg), room air saturation was only 88% and kept on 4L oxygen support. The abdomen was soft but distended, bowel sounds were sluggish, clinically free fluid was appreciated. Ryle's tube aspiration produced 700 ml bilious aspirate.

Table 1: Initial Investigations

	At admission	On the day of decompensation	Post corticosteroid therapy
Complete Blood Counts			
Hemoglobin (g/dL)	13.9	12.3	9.3
WBC count (cells/µL)	6000	16000	14000
Neutrophils (%)	66.6%	85.5	83.4
Lymphocyte (%)	20.7	7.5	9.4
Monocyte (%)	12.3	6.1	4.9
Eosinophil (%)	0.3	0.9	2.2
Basophil (%)	0.1	0	0.1
Platelet (cells/µL)	7000	161,000	152,000
ESR	15	NA	NA
Prothrombin time (s)	11	12.4	NA
INR	1.05	1.18	NA
Liver Function Tests			
Total bilirubin (mg/dL)	1.9	0.6	0.8
Indirect/ direct (mg/dL)	1.6/1.3	0.4/0.2	0.4/0.4
SGPT (U/L)	46	38	130
SGOT (U/L)	30	45	43
ALP (U/L)	60	49	59
Total protein (g/dL)	6.3	6.8	5.9
A/G (g/dL)	3.3/3	3.6/3.2	3.3/2.4
GGT(U/L)	174	188	187
Procalcitonin (ng/mL)	0.250	0.255	NA
Lipase (U/L)	21	NA	NA
Amylase(U/L)	36	NA	NA
Renal function tests			
Urea (mg/dL)	52	47	34
Creatinine (mg/dL)	1.27	0.81	0.45

Table 2: Ascitic Fluid Analysis

	At admission	On the day of decompensation
Color	Pale yellow, slightly cloudy	Pale yellow slightly cloudy
Total count	430 cells/ cu.mm	790 cells/cu.mm
Neutrophils	31%	44%
Lymphocytes	13%	16%
Monocytes/ Macrophages	56%	40%
Mesothelial cells	Few	++

Table 3: Pleural Fluid Analysis

Color	Pale yellow
Total count	620 cells/ cu.mm
Neutrophils	8%
Lymphocytes	10%
Eosinophils	2%
Monocytes/ Macrophages	80%
Protein	4 g/dL
Albumin	2.45g/dL
ADA	9.6 U/L

Initial investigation (Table 1) revealed a severe thrombocytopenia, with a normal total and differential count. Urea and creatinine levels were mildly elevated. Liver function tests showed a slight elevation of serum total bilirubin levels. Amylase and lipase levels were normal. Serology was negative for hepatitis B antigen (HBsAg), Anti HCV and HIV antibodies. Dengue serology was positive for IgG antibody but negative for IgM antibody. Chest radiograph showed minimal pleural effusion. No air fluid levels seen in erect abdomen radiograph. Ultrasound abdomen showed moderate ascitis and minimal pleural effusion. Ascitic fluid total counts were elevated with atypical monocytic predominance (Table 2). It was a high protein low serum ascitic albumin gradient type of ascitis suggestive of peritoneal involvement. Pleural fluid total counts were elevated with monocytosis and presence of mesothelial cells (Table 3). Pleural fluid ADA level was normal. Pleural fluid cytology showed inflammatory cells composed of neutrophils, lymphocytes and anthracotic pigment laden macrophages, consistent with suppuration. Sinus tachycardia with low voltage complexes were seen in ECG but echocardiogram and Troponin T were normal. Serum procalcitonin was not elevated. Blood cultures, ascitic and pleural fluid cultures were sterile. AFB staining for tubercular bacilli and Gene Xpert MTB-RIF was negative ruling out tubercular cause. On further evaluation, abdominal Computed Tomography (CT) scan showed left mild to moderate pleural effusion, bilateral atelectasis and moderate fatty liver, omental fat stranding was seen and edematous wall in the distal ileal loops showing luminal narrowing.

Patient continued to have fever spikes and tachycardia was persistent throughout the hospital stay. On the 4th day of admission his clinical condition went for decompensation requiring mechanical

ventilation. He was treated with antibiotics for secondary infection and other supportive measures. Repeat procalcitonin level (Table 1) was normal, cultures continued to be sterile. This suggested a possible autoimmune cause but on further investigation ANA – immunofluorescence, ANA profile and ANCA profiles were negative, RA factor was negative. At this time the histopathology report of the lymph node biopsy showed a typical histology of Kikuchi's disease. A pulse therapy of high dose intravenous steroids was started following which patient showed a remarkable response. He was extubated and continued on nasal oxygen within two days of initiation of therapy. Platelet counts, total counts, kidney function, tachypnea and tachycardia improved and fever spikes settled. The patient was switched to oral steroid therapy and did well.

Discussion

Kikuchi Fujimoto disease (KFD) was first described by Kikuchi [1] et al and Fujimoto [2] et al independently in 1972, Japan. KFD is a perplexing disease due to its wide range of clinical manifestations and no definitive etiology. Typically, it is described as a sub-acute lymph node enlargement in association with low grade fever. It is also known as Histiocytic Necrotising Lymphadenitis for its defining histopathological features, a mononuclear hypercellular response with variable necrosis [3,4].

KFD is very rare typically said to occur in young females of Asian descent. Although more frequent in Asians, it has been reported in all population groups. The age at presentation usually is less than 40 years. There is a female predominance among adults, anywhere from 1:4 to 1:1 male to female ratio has been reported. A male predominance among children is noted in the pediatric age group [5,6,7].

In the retrospective analysis done by Dumas et al and In Young Joung et al, patients more frequently present with unilateral cervical lymphadenopathy involving the posterior cervical triangle [6,7]. Fever, myalgias, arthalgia are the most common presenting symptoms. Patients also had associated cutaneous rash, night sweats, and weight loss. Tender lymphadenopathy and autoimmune associations are more frequent in womenand severe presentations are seen more in men. Cutaneous rash, weight loss, arthalgia are associated with SLE. The syndrome in classical cases is benign, self limiting, lasting for around one to four months and requiring no more than supportive therapy alone. Recurrence is rare anywhere from 20%- 3% [5,7].

Various theories have been proposed to explain the etio-pathogenesis of the disease. It is thought to be a self limiting hyper-immune response to agents like viruses or physio-chemical agents. Viruses like Epstein Barr Virus (EBV), Herpes-viruses 6 and 8, Herpes simplex virus, Human immunodeficiency virus and other infectious agents like Yersenia pestis and Toxoplasma have been suggested as the etiology. A viral etiology has been justified based on the clinical prodrome, atypical blood picture and poor response to antibiotics but no consistent evidence has been put forth. Other theories suggest that KFD may be an incomplete autoimmune phenomenon which may or may not evolve into a full blown autoimmune disease. The association of SLE with KFD supports this theory. KFD has also been associated with some HLA (Human Leukocyte Antigen) phenotypes, which can explain a familial predisposition in rare cases and its higher frequency in some ethnic groups. Though many points support these theorized none have been established as the cause for the disease [4,5].

There is no pathognomonic feature of KFD in blood investigations, but studies have noted

leucopenia, elevated serum Lactate Dehydrogenase and thrombocytopenia in these patients [5-7]. Only definitive investigation for diagnosis is lymph node biopsy and histopathology. The typical histopathological feature in case of KFD is effacement of architecture of the lymph node, paracortical apoptotic necrosis with presence of histiocytes, plasmacytoid cells interspersed by karyorrhectic debris and without formation of granulomas. Crescentic histiocytes are present in the necrotic foci with clustering of the plasmacytoid dendritic cells at the margins of the necrotic foci. There may be a mix of lymphocytes present some of them may be large with tingible body macrophages giving a false appearance of lymphoma. Kuo et al have divided the histopathological findings in KFD into proliferative, necrotizing and xanthomatous types [3]. Immunohistochemistry is used along with histopathology for diagnosis and for differentiation from malignant lymphomas [3-5]. The predominance of CD8 positive lymphocytes, myeloperoxidase, lysozyme, CD68 and CD4 in histiocytes is considered a marker for KFD along with absence of neutrophils. FNAC can show approximately 50% accuracy in selected cases of lymphadenopathy and sometimes can be useful independently as a means of diagnosis if typical clinical features are present [5]. Imaging studies like ultrasonography, computed tomography and FDG-PET scans find their use in evaluation of lymphadenopathy especially in generalized disease. Studies to determine the characteristic imaging patterns of KFD induced lymphadenopathy have been published but have yet to be accepted as a reliable means of diagnosis [5,6].

The diagnosis of Kikuchi's disease can be confounding due to its varied presentations. The possibility of misdiagnosis is high, as other more common disease present similarly. Moreover, the only definitive means of diagnosis is lymph node biopsy. The main differentials are Tuberculosis, Malignant lymphoma and SLE lymphadenitis. Cases of KFD mimicking acute appendicitis, malignant papillary carcinoma of thyroid have been published. There have also been reports of high rates of misdiagnosis in the past. One such article reports a 40% chance of misdiagnosis, a false diagnosis of malignant lymphoma was made [8]. With greater awareness of the disease and improving imaging studies misdiagnosis may have reduced. KFD may also be under-diagnosed as a mild episode can be attributed to probable infectious or reactive cause without further evaluation.

Accurate diagnosis becomes challenging especially when the presentation is atypical. Varied atypical manifestations of KFD have been reported. Extra-nodal involvement of KFD is associated with greater severity and duration of disease. There have been reports of Kikuchi-Fujimoto disease causing pleural effusion and interstitial lung disease, cryptogenic organizing pneumonia, autoimmune hepatitis, panuveitis and aseptic meningitis [6,9]. There is a strong association of KFD with Systemic Lupus Erythematosis, 13-25% of patients with KFD also developed SLE [6]. Kikuchi's disease can occur before, during and after the onset of SLE [5]. KFD has also been reported in association with autoimmune diseases like Rheumatoid arthritis, Sjogren's syndrome, Anti-phospolipid antibody syndrome, relapsing polychondritis multiple connective tissue disorder and others [9].

In contrary to the classical, benign cases of KFD, there are reports of fatal disease. In these extremely rare cases, death occurred due to disseminated intravascular coagulopathy, pulmonary hemorrhage and hemophagocytic syndrome [10].

In this case for discussion, the main working diagnosis was sepsis of probable gastrointestinal origin. A severe case of Kikuchi's disease mimicking sepsis with generalized serositis without an

autoimmune association is unheard of. This may suggest that KFD can occur independently without an autoimmune trigger. A case was reported of a female patient with histopathology suggesting KFD developed ascitis and plural effusion which progressed into a case of SLE [11]. In another report two cases with mixed connective tissue disorder develop KFD presenting similar to sepsis [12]. This also emphasizes the need for long term follow up for this patient to review autoimmune status.

Accurate diagnosis is essential in choosing the line management, as this is hugely different from that of its differentials. Hence, a diagnosis of KFD in any case with fever and lymphadenopathy should always be kept in mind.

The treatment of KFD is mostly symptomatic. Till present no guideline has been established for treatment of Kikuchi- Fujimoto disease. Good results have been documented with use of steroids in case of severe KFD. Others such as hydroxychloroquine, intravenous immunoglobulin and a combination therapy have been tried in cases of refractory or recurrent disease [6,12]. Although, a good response to treatment and prognosis is seen, a case refractory to treatment has been reported. A quick improvement in the general condition was seen in our patient after administration of steroids and he remains sero-negative in follow-up for 6 months following remission.

Conclusion

In conclusion, Kikuchi Fujimoto disease though rare, should always be on the list of differentials for any case of fever with lymphadenopathy. Despite being benign, KFD can present with severe manifestations. So, accurate diagnosis is indispensible in treatment of such patients.

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