Case Report
A Case of Relapsing Kikuchi-Fujimoto Disease

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Kikuchi-Fujimoto disease (KFD) or histiocytic necrotizing lymphadenitis was first described in Japan in 1972 [1, 2]. It has been described as a benign syndrome most commonly involving cervical lymphadenopathy, fever, and night sweats. The etiology of KFD is unknown but it is thought to be triggered by an autoimmune or viral process with an exaggerated T-cell-mediated immune response. KFD can mimic other serious conditions such as lymphoma, systemic lupus erythematosus (SLE), herpes simplex, and Epstein Barr virus. Diagnosis is confirmed histopathologically. Kikuchi’s disease is typically reported to have a self-limiting course, resolving within several months and with a low recurrence rate between 3% and 4%. There is no specific treatment for KFD but any treatment is generally directed towards symptomatic relief with antipyretics and anti-inflammatory medications. In severe cases corticosteroids have been used. Here we describe a case of a previously healthy 26-year-old female that presented with fever and cervical lymphadenopathy. Malignancy and infections were ruled out, and she was diagnosed with KFD histopathologically by lymph node biopsy. Her case is a severe case of KFD that despite treatment with multiple courses of corticosteroids and an immune modulating agent, relapsed.

1. Introduction

Kikuchi-Fujimoto disease (KFD) or histiocytic necrotizing lymphadenitis was first described in Japan in 1972 [1, 2]. It has been described as a benign syndrome most commonly involving cervical lymphadenopathy, fever, and night sweats. The etiology of KFD is unknown but it is thought to be triggered by an autoimmune or viral process with an exaggerated T-cell-mediated immune response. KFD can be mistaken with other serious conditions such as lymphoma, systemic lupus erythematosus (SLE), herpes simplex, and Epstein Barr virus, to name a few. Diagnosis is confirmed histopathologically. Kikuchi’s disease is typically reported to have a self-limiting course, resolving within several months and with a low recurrence rate between 3% to 4% [3]. There is no specific treatment for KFD but any treatment is generally directed towards symptomatic relief with antipyretics and anti-inflammatory medications. In severe cases, corticosteroids have been used without relapse of disease. Here we present a severe case of KFD that recurred despite multiple doses of corticosteroids and an additional immune modulating agent.

2. Case Presentation

An otherwise healthy 26-year-old African American female presented with progressive fever, headache, facial edema, and periorbital swelling of 3 weeks duration. She also complained of nausea, decreased appetite, and back pain. She had daily fevers up to 104.1°F with associated tachycardia. On physical exam, she had significant facial and periorbital swelling, preauricular, and anterior cervical tender lymphadenopathy. There was no evidence of scleral icterus or hepatosplenomegaly. Her complete blood count revealed a pancytopenia with a WBC count of 2,000 cells/mm³ and the presence of 1% atypical lymphocytes with an increase in immature neutrophils (“bands”), a hemoglobin of 11.3 g/dL, and a mild thrombocytopenia. Additional testing revealed elevated transaminases. An erythrocyte sedimentation rate (ESR) at time of her initial presentation was minimally elevated. C-reactive protein (CRP), antinuclear antibody (ANA), and angiotensin converting enzyme (ACE) were all normal, as shown in Table 1.

Computer tomography (CT) imaging of her neck was performed and revealed abnormally enhancing cervical and
Table 1: Pertinent laboratory data at the time of the patient’s initial evaluation.

| Test                        | Admission value | Reference range   |
|-----------------------------|-----------------|-------------------|
| Albumin (g/dL)              | 3.6             | 3.5–5.2           |
| Total protein (g/dL)        | 6.7             | 6.6–8.7           |
| AST (U/L)                   | 145             | 10–50             |
| ALT (U/L)                   | 74              | 10–50             |
| Alkaline phosphatase (U/L)  | 54              | 40–130            |
| Total bilirubin (mg/dL)     | 0.8             |                   |
| WBC (per mcL)               | 2,000           | 4,500–11,000      |
| Hemoglobin (g/dL)           | 11.3            | 12.0–15.0         |
| Hematocrit (%)              | 34.0            | 36–48             |
| Platelets (per mcL)         | 126,000         | 150,000–450,000   |
| ESR (mm/hr)                 | 23              | 0–20              |
| CRP (mg/dL)                 | 0.63            | <0.80             |
| ANA                          | Negative        | Negative          |
| ACE (U/L)                   | 58              | 9–67              |

Key: AST: aspartate aminotransferase; ALT: alanine aminotransferase; WBC: white blood cell; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; ANA: antinuclear antibody; ACE: angiotensin converting enzyme.

With her history suspicious for lymphoma, an MR I of the brain was obtained that revealed posterior leptomeningeal enhancement concerning for possible meningitis or lymphoma. Cerebral spinal fluid obtained by lumbar puncture however did not demonstrate findings consistent with meningitis or neoplasia. An excisional cervical lymph node biopsy and bone marrow aspiration and biopsy were performed. The bone marrow biopsy revealed a slightly hypocellular marrow for age with trilineage hematopoiesis and less than 1% blasts. There were increased marrow histiocytes with focal evidence of hemophagocytosis and lymphohistiophagocytosis. The flow cytometry of the bone marrow was negative for lymphoma or leukemia and revealed a lymphoid population of approximately 14% of the nucleated/nonerythroid cells, of which 83% were T cells and 8% were polyclonal B cells. Despite the information provided by the bone marrow biopsy, a specific diagnosis was not reached.

Excisional cervical lymph node biopsy was performed with results that confirmed a diagnosis of Kikuchi-Fujimoto’s disease. The hematoxylin and eosin staining showed disrupted architecture, paracortical expansion with areas of necrosis and nuclear debris (thin arrow). Plasma cells and numerous histiocytes (thick arrows) present. Above findings are consistent with KFD.

This patient was started on prednisone 60 mg daily with rapid improvement in her lymphadenopathy, fevers, and other constitutional symptoms. She continued high dose corticosteroids with a slow taper over several months; however, after four months and reaching a dose of 5 mg a day of prednisone her symptoms relapsed necessitating reinitiation of high dose prednisone. Repeat serologic screening for
systemic lupus erythematosus with an ANA was negative. Although symptoms improved with resuming a high dose of prednisone, her course was complicated by development of glucocorticoid-induced osteoporosis. Subsequently, she was started on hydroxychloroquine with a rapid steroid taper. She continues to be on hydroxychloroquine for symptom control but also experienced a relapse of her symptoms while on this medication and is currently being considered for dual immunosuppressive therapy to control her condition.

3. Discussion

Kikuchi-Fujimoto disease (KFD) is most commonly seen in adults younger than 40 years of age. A female predominance has been reported previously but recent reports reveal a ratio closer to 1:1 for males and females [2]. It has the highest prevalence in patients of Asian descent. The onset of KFD can be acute or subacute developing over several weeks. The majority of patients (56% to 98%) present with cervical lymphadenopathy. The next most common clinical manifestation is fever which occurs in 30% to 50% of affected patients [2]. Other less commonly reported findings included leukopenia (up to 50%), atypical lymphocytes on peripheral smear, liver dysfunction, and bone marrow involvement [1, 2]. Some viral infections such as Ebstein-Barr virus or human herpes virus 6 have been suggested as triggers for the onset of KFD but this hypothesis has not been confirmed. There have been case reports of patients concurrently developing the hemophagocytic syndrome and these two syndromes may be part of a continuum rather than two separate entities [2].

The diagnosis of KFD is made histopathologically typically from tissue obtained by excisional lymph node biopsy. Histopathological findings for KFD include irregular paracortical areas of coagulative necrosis with extensive karyorrhectic debris and altered lymph node architecture [1–3]. There is an abundance of histiocytes and plasmacytoid monocytes with a relative absence of neutrophils. The majority of the lymphocyte population are T cells with few B cells present. Of those T cells, there is CD8+ predominance.

Clinically KFD can mimic lymphoma. Also to consider in the differential diagnosis are infectious etiologies such as mononucleosis, tuberculosis, herpes simplex virus, and SLE. As the treatment for each possible etiology is very different, correct diagnosis of KFD is important [1, 2]. It has been hypothesized that individuals with KFD are more susceptible to SLE and should be routinely screened for this disorder [1, 4].

Most reports describe KFD as a benign self-limited syndrome with effective symptomatic treatment provided by anti-inflammatory and antipyretics. Glucocorticoids are typically used for symptomatic relief in severe cases [1, 4, 5]. Signs and symptoms related to KFD usually resolve after several months [1–5]. A low recurrence rate of 3% to 4% has been reported [1–3]. Recurrences have been treated

### Table 2: Pertinent infectious serologies performed during the patient’s evaluation.

| Serology                              | Result       | Reference Range                  |
|---------------------------------------|--------------|----------------------------------|
| Epstein-Barr Virus capsid Ab IgG      | Positive     | Negative                         |
| Epstein-Barr Virus capsid Ab IgM      | Negative     | Negative                         |
| Epstein-Barr Virus Nuclear Ab IgG     | Positive     | Negative                         |
| Mononucleosis                         | Negative     | Negative                         |
| Cytomegalovirus Ab IgG                | Positive     | Negative                         |
| Cytomegalovirus Ab IgM                | Negative     | Negative                         |
| Human immunodeficiency virus          | Negative     | Negative                         |
| Adenovirus Ab                         | 1:16 Ab detected | <1:8 Ab not detected |
| Parvovirus B12 IgG                    | <0.1         | <0.9 Negative                    |
| Parvovirus B12 IgM                    | 0.1          | <0.9 Negative                    |
| Coxiella burnetii Ab                  | Negative     | Negative                         |
| Hepatitis C Ab                        | Negative     | Negative                         |
| Hepatitis A Ab                        | Negative     | Negative                         |
| Hepatitis B surface Ag and core Ab    | Negative     | Negative                         |
| Aspergillus niger Ab                  | Negative     | Negative                         |
| Aspergillus fumigatus Ab              | Negative     | Negative                         |
| Aspergillus flavus Ab                 | Negative     | Negative                         |
| Blastomyces species Ab                | Negative     | Negative                         |
| Coccidioides immitis Ab               | Negative     | Negative                         |
| Histoplasma capsulate mycelium Ab     | <1:8         | <1:8 Negative                    |
| Histoplasma capsulate mycelial Ab     | <1:8         | <1:8 Negative                    |
| Toxoplasma gondii Ab IgG and IgM      | Both negative| Negative                         |
| Bartonella henselae Ab IgG and IgM    | Both negative| Negative                         |
| Bartonella quintana Ab IgG and IgM    | Both negative| Negative                         |

Key: Ab: antibody; Ag: antigen.
with the same agents as the first occurrence. Rezai et al. reported the first case report of recurrent KFD treated with hydroxychloroquine lieu of using glucocorticoids [4].

Our patient did not have a benign, self-limited course. Her disease was complicated by immediate return of symptoms after 4 months of glucocorticoid therapy and before complete discontinuation. Furthermore, she experienced glucocorticoid-induced osteoporosis. Hydroxychloroquine was initiated as alternative to glucocorticoids because of its safer side effect profile. She continues to require treatment with hydroxychloroquine but as noted above has experienced a relapse of her disease on this agent and will likely need dual immunosuppressive therapy in the very near future.

Disclosure

T. Rezayat affirm that this paper has neither been submitted nor is simultaneously being submitted elsewhere. No portion of the data has been or will be published in proceedings or transactions of meetings or symposium volumes. T. Rezayat affirm that neither her nor the coauthors have no financial support or other benefits from commercial sources to disclose. The authors received no pharmaceutical or industry support in writing this paper.

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