Kikuchi–Fujimoto disease: a case report of a multi-drug resistant, grueling disease

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Abstract

Histiocytic necrotizing lymphadenitis or Kikuchi–Fujimoto disease (KFD) is characterized by its rare occurrence. Mostly prevalent among Asian women, KFD manifests with lymphadenopathy—affecting mostly cervical and rarely generalized or retroperitoneal regions—in addition to fever. It is a self-limited disease that resolves within 1–4 months, responding remarkably to glucocorticosteroids or hydroxychloroquine. However, some rare cases prove to be unresponsive to the previously mentioned therapies. Here is a description of a case of KFD affecting a 67-year-old Syrian woman with a history of hypothyroidism due to iodine-deficiency. The patient’s initial clinical picture was malaise, fever, pericarditis and generalized lymphadenopathy. As treatment, she was given glucocorticosteroids with no significant response, while hydroxychloroquine proved to be partially effective. Until the date of this report, she has been receiving hydroxychloroquine with only slight clinical improvement. This case is proving to be resistant unlike most KFD cases that generally respond very well to treatment.

INTRODUCTION

Kikuchi–Fujimoto disease (KFD), or histiocytic necrotizing lymphadenitis, is a sub-acute necrotizing lymphadenitis of an indefinite etiology. Mostly prevalent among young Asian women, it is usually a self-limited disease with excellent response to therapy [1]. It carries a long-term risk of recurrence or progression to systemic lupus erythematosus (SLE) [2]. Here is the description of the case with a severe and poorly responsive form of this disease.

CASE REPORT

Our patient is a 67-year-old Syrian woman, with a history of iodine-deficiency hypothyroidism and angioedema occurring 20 years ago. She initially presented with malaise, fatigue, arthralgia, fever, night sweats, anorexia and weight loss. Physical examination showed a fever of 38°C and mild hepatomegaly. Her family history is negative for autoimmune diseases. The initial laboratory results are available in (Table 1). For a period of 1 month, she took paracetamol and other NSAIDs without any clinical response. Afterwards, she started complaining of vague chest pain. Echocardiography revealed mild reactive pericardial effusion, and pericardial thickening. Then 15 days later, she complained of painful cervical nodes. Physical examination showed then a tender, mobile, bilateral cervical and axial lymphadenopathy. The cervical ultrasound demonstrated massive bilateral and mild (<10 mm) retroperitoneal lymph node enlargements (Fig. 1). She underwent an excisional cervical lymph node biopsy for pathological evaluation. As a result, microscopic findings demonstrated partial effacement of lymph node architecture by paracortical expansion composed of numerous histiocytes of different types at the edge of the necrotic foci. These histiocytes are bland in appearance, including both non-phagocytic and phagocytic forms. The so-called crescentic...
histiocytes were also seen. There were small-sized lymphoid follicles in the cortical and paracortical areas with germinal centers and sinus histiocytosis. The latter contained clusters of plasmacytoid dendritic cells admixed with large transformed lymphocytes of immunoblast morphology. There was no granuloma and Ziehl–Neelsen Stain was negative, which excluded granulomatous lymphadenitis such as TB or Sarcoidosis. No cellular atypia was noted in the limits of the examined biopsy (Fig. 3). Immune stains revealed positivity for CD 68 and S-100, whereas CD1a was negative (Fig. 4). Due to the afore-mentioned findings, she was diagnosed with KFD. Consequently, the patient started prednisolone therapy with a dose of 1 mg/kg. Her lymphadenopathy resolved completely, but her clinical symptoms did not improve. After 11 months of prednisolone therapy, there was

### Table 1: Laboratory values and treatment regimens throughout the disease course.

| Treatment | NSAID | Initiation of prednisolone | Initiation of hydroxychloroquine | Units |
|-----------|-------|-----------------------------|---------------------------------|-------|
|           | 28/4  | 11/7                        | 11/4                            |       |
| 2015      | 1/6   | 8/8                         | 19/6                            |       |
| 16/6      | 16/2  | 14/8                        | 14/8                            |       |
| RBC       | 3.8   | 3.5                         | 3.7                             | MIL/UL|
| HGB       | 10.6  | 9.2                         | 9.5                             | G/DL  |
| WBC       | 14.1  | 17                          | 13.1                            | K/UL  |
| NEU       | 80%   | 89%                         | 82%                             |       |
| LYM       | 13%   | 10%                         | 17%                             |       |
| Mono      | 5%    | 2%                          | 1%                              |       |
| PLT       | 350   | 310                         | 244                             |       |
| ESR 1st hour | 100  | 80                          | 75                              |       |
| CRP       | 35    | 100                         | 70                              |       |
| ANA       | Neg   | Neg                         | Neg                             |       |
| ANCA c    | Neg   | Neg                         | Neg                             |       |
| ANCA p    | Neg   | Neg                         | Neg                             |       |
| RF        | 0.1   | 1.9                         | 8                               | IU/ML |
| IGRA      | Neg   | Neg                         | Neg                             |       |
| CMV IgG   | Pos   | Pos                         | Pos                             |       |
| EBV IgG   | Pos   | Pos                         | Pos                             |       |
| Widal test| Neg   | Neg                         | Neg                             |       |
| Malaria organism detection | Neg | Neg                         | Neg                             |       |
| Cryoglobulins | Neg | Neg                         | Neg                             |       |

RBC: red blood cells, HGB: hemoglobin, WBC: white blood cells, NEU: neutrophils, LYM: lymphocytes, Mono: monocytes, PLT: platelets, ESR: erythrocytes sedimentation rate, CRP: C-reactive protein, ANA: anti-nuclear antibodies, ANCA c: anti-neutrophil cytoplasmic antibodies cytoplasmic, ANCA p: anti-neutrophil cytoplasmic antibodies perinuclear, RF: rheumatoid factor, IGRA: interferon gamma release assay.

Figure 1: Cervical echography demonstrating enlarged lymph nodes. Black arrows point to the enlarged nodes.

Figure 2: Axial CT of the upper thoracic region showing axillary lymphadenopathy. Black arrows point to the enlarged lymph nodes.
no significant clinical response. Prednisolone therapy was, therefore suspended. Afterwards, she started therapy with hydroxychloroquine. Until the date of this report, after 5 months of treatment, she has experienced only partial clinical response. Her follow-up laboratory results are available in (Table 1).

DISCUSSION

KFD was first described in Japan in 1972. Since then, the total patient count has been 733 cases [1]. KFD affects all ages with a mean of 21 [2]. It occurs in many regions, most frequently in Asia and particularly in Nepal. Medical literature contains KFD reports from Syria’s neighboring countries [3, 4]. However, this is the first report from Syria.

There are two possible etiologies: viral and autoimmune. Viral etiology comprises a hyper-immune reaction in genetically predisposed patients. In contrast, autoimmune etiology is
taken into consideration because of the correlation between KFD and autoimmune diseases. Many reports even refer to KFD as an earlier stage of SLE [2]. In this study, ANA and ANCA tests proved negative excluding SLE diagnosis.

Until today, there has been no definite treatment for KFD. Systemic symptoms and lymphadenopathy usually resolve within 1–4 months. Recurrence occurs up to 8 years after the first episode in 4–15% of patients. KFD has a fatality rate of 0.5–2.1% [1, 2]. It may sometimes progress to SLE. Consequently, follow-up is generally advisable. Due to its self-limiting course, the most common approach is patient observation. Patients with mild symptoms usually respond to treatment with NSAIDs and anti-pyretic drugs. In contrast, patients with extra nodular involvement, such as the CNS and lungs, usually respond to short pulses of corticosteroids. Unresponsive patients or patients with complicated diseases may respond to treatment with hydroxychloroquine or glucocorticosteroids. The final treatment, which was not possible in this case, includes alternating high-dose glucocorticosteroids and IV immunoglobulin [1]. There have been two reports of impressive improvement to hydroxychloroquine [5, 6]. However, a report of an unresponsive patient who consequently died of DIC is there as well [4]. In summary, our patient was clinically unresponsive to glucocorticosteroids, and was partially responsive to hydroxychloroquine. This unresponsive form of the disease could be a starting point for further investigations.

KFD usually manifests with lymphadenopathy, which is tender in up to 59% of patients, while cervical lymph nodes are most commonly affected and unilateral in 88.5% [2]. Other nodal involvements include axillary, retroperitoneal, inguinal, and mesenteric lymph nodes. The nodes sizes vary from 0.5 to 3.2 cm [7]. Our patient had bilateral cervical, axillary, and retroperitoneal lymph node involvement. Therefore, she had generalized lymphadenopathy, which is an uncommon finding that occurs in only 1–22% of cases [2].

KFD is a rare disease that sometimes proves to be a diagnostic dilemma. It should be included in the differential diagnosis of lymph node enlargement because its therapy dramatically differs from other causes. For example, misdiagnosis can lead to unnecessary chemotherapy [2, 7]. KFD’s differential diagnosis includes infections, Granulomatous lymphadenitis, connective tissue diseases, and lymphoproliferative disorders [2, 4].

What is peculiar about this case is the association between KFD, hypothyroidism and pericarditis about which similar cases have been reported [8]. Concerning hypothyroidism, the literature review reveals two cases: one with iatrogenic hypothyroidism and the other with Hashimoto thyroiditis [9, 10]. In this case report, a relation between KFD and hypothyroidism is excluded, as both the latter cases do.

This is the first Syrian KFD case report; it is distinct in its poor response to therapy, presence of generalized lymphadenopathy, and association with hypothyroidism and pericarditis. It appears that there are two forms of KFD: a responsive form and an unresponsive one, as our case suggests. KFD should be considered as a lymphadenopathy differential diagnosis, and patients should be followed up for possible SLE development.

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**CONFLICTS OF INTEREST**

The authors declare no conflicts of interest.

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No ethical approval is needed.

**CONSENT**

It has been obtained.

**GUARANTOR**

The authors nominate Alexey Youssef as a guarantor.

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