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CASE REPORT

Kikuchi-Fujimoto Disease, A Case Report from Australia

Cecilia Gu[1] and Sherman Gu[2*]

[1]*Monash University Medical Student, Australia*

[2]*Registered Chinese Medicine Practitioner, Knox Chinese Healing and Myotherapy, Australia*

***Corresponding author:** *Sherman Gu, Registered Chinese Medicine Practitioner, Knox Chinese Healing and Myotherapy, 285 Stud Road, Wantirna South Victoria 3152, Australia, Tel: +6139-8003-969*

Abstract

Kikuchi-Fujimoto disease (KFD), also known as Kikuchi's disease or histiocytic necrotising lymphadenitis, is a rare and benign medical condition of unknown aetiology. It is often misdiagnosed as lymphoma or systemic lupus erythematosus (SLE), leading to inappropriate investigations and delayed treatment. It is thus important for clinicians to be cognizant of this condition when assessing patients with cervical lymphadenopathy. This case report outlines the clinical course and treatment of a 52-year-old Chinese woman who presented to her general practitioner (GP) and later the emergency department with cervical lymphadenopathy and general malaise. A lymph node biopsy revealed a diagnosis of KFD, and she was treated with prednisolone and hydroxychloroquine with full remission of symptoms after two months. Clinicians should hold a high degree of suspicion of KFD for young women who have cervical lymphadenopathy, especially those of oriental origin.

Keywords

Kikuchi-Fujimoto disease, KFD, Kikuchi's disease, Histiocytic necrotising lymphadenitis

Abbreviations

ANA: Antinuclear Antibodies; anti-dsDNA: Anti-Double Stranded Deoxyribonucleic Acid; BCL2: B-Cell Lymphoma 2; CMV: Cytomegalovirus; CRP: C-Reactive Protein; CT: Computed Tomography; EBV: Epstein-Barr Virus; ENA: Extractable Nuclear Antigen; ESR: Erythrocyte Sedimentation Rate; FBE: Full Blood Examination; GP: General Practitioner; HSV: Herpes Simplex Virus; HTLV: Human T-Lymphotropic Virus; IL-6: Interleukin 6; KFD: Kikuchi-Fujimoto Disease; LFT: Liver Function Tests; PCR: Polymerase Chain Reaction; SLE: Systemic Lupus Erythematosus; UEC: Urea Electrolytes and Creatinine.

Introduction

Kikuchi-Fujimoto disease (KFD), also known as Kikuchi's disease or histiocytic necrotising lymphadenitis, is a rare condition that was first described in Japan in 1972 and is characterised by fever and cervical lymphadenopathy [1]. It is known to occur mostly in individuals of Asian descent though has now been recognized in various countries and ethnic groups. There remains, however, scant documentation of KFD cases in Australia amongst the existing literature. This case report describes a 52-year-old Chinese woman who presented to her general practitioner (GP) in Australia with painful lymphadenopathy and malaise and was eventually diagnosed with KFD after biopsy specimens revealed characteristic findings. The purpose of this article is to alert health professionals to the possibility of KFD as a differential in those with cervical lymphadenopathy, particularly in young women of Asian descent, which make up a sizeable proportion of the population in Australia.

Case Presentation

A 52-year-old Chinese woman presented to a GP in May 2021 with a one-month history of fatigue, general malaise and painful bilateral cervical lymphadenopathy. This was associated with unintentional weight loss of three kilograms, reportedly due to the pain inhibiting effective oral intake. There were no focal infective symptoms apart from some dry cough prior to her presentation. She did not experience any night sweats and there were no symptoms suggestive of SLE such alopecia, mucosal ulcers, rashes, arthralgia or previous serositis. The patient was otherwise healthy with no

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significant past medical history or family history. In terms of the patient's social history she had immigrated from China 15 years ago and did not smoke, drink alcohol nor take any recreational drugs.

A full blood examination (FBE) revealed leukopenia (from 4.8 to 2.7 × 10^9/L, normal range 4.0-11.0 × 10^9/L) and neutropenia (from 3.1 to 1.9 × 10^9/L, normal range 2.0-8.0 × 10^9/L). Antibody serology tests for cytomegalovirus (CMV) and Epstein-Barr virus (EBV) showed no active infection. Other laboratory tests were performed including urinalysis which showed increased erythrocytes (84 × 10^6/L, normal range < 10 × 10^6/L). Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were mildly elevated at 44 mm/hr (normal range < 20 mm/hr) and 17 mg/L (normal range 0-10 mg/L) respectively.

The patient visited a Chinese medicine clinic for Chinese herbal medicine treatment and eventually was referred to the emergency department by her GP who trialled her on two courses of antibiotics with no effect. Subsequently she was admitted under the hematology unit for eight days, during which fevers of up to 39.5 ˚C were recorded. Further investigations were performed including blood cultures, antinuclear antibodies (ANA), extractable nuclear antigen (ENA) antibodies, anti-double stranded deoxyribonucleic acid (anti-dsDNA) antibodies, complement levels, hepatitis serology and tuberculosis polymerase chain reaction (PCR), all of which were unremarkable. A blood film to rule out haematological malignancies was ordered and showed neutropenia with a left shift and mild toxic granulation along with unremarkable lymphocyte morphology with only a very occasional reactive lymphocyte seen. A computed tomography (CT) scan on the neck and chest was performed and found mildly enlarged bilateral submandibular nodes that measured 1.4 cm and 1.2 cm in short axis dimension on the right and left side respectively as well as slightly prominent bilateral jugulodigastric nodes measuring 1.1 cm in short axis dimension on both sides. Such findings were considered non-specific but favored a reactive rather than neoplastic process.

An ultrasound-guided biopsy of a left submandibular lymph node was subsequently performed. Histological examination revealed sections in which the normal architecture had been replaced by a diffuse mixed cellular infiltrate with areas of fibrinoid necrosis. There was a mixture of small lymphocytes, large lymphoid cells and many histiocytes with abundant apoptotic debris and areas of frank necrosis without significant numbers of neutrophils. These findings were consistent with KFD and, with rheumatology input; the patient was commenced on a course of oral prednisolone 15 mg daily and hydroxychloroquine 200 mg daily in addition to paracetamol and ibuprofen which she had been taking for analgesia. She was discharged from hospital a few days later.

Two months after her initial presentation, the patient reported complete resolution of her symptoms. Repeat blood tests (FBE, Urea Electrolytes and Creatinine [UEC], liver function tests [LFT], CRP, ESR) showed no abnormalities and she was reviewed as an outpatient at the rheumatology clinic where she was advised to continue hydroxychloroquine and reduce the prednisolone dose over several weeks until her next appointment.

Discussion

Epidemiology

KFD is a rare condition that was first reported independently by Kikuchi and Fujimoto in 1972 [2]. It is known to occur mostly in individuals of Asian descent and was initially described in Japan. KFD tends to affect younger populations [3] and is thought to be more prevalent in females, with a 2017 cohort study revealing a female to male ratio of 2.9:1 [1].

Aetiology and pathogenesis

The aetiology of KFD remains largely unknown. Several viral agents have been investigated as potential triggers for the condition, the most notable being EBV, human herpesvirus (HHV) types 6, 7 and 8, HIV, herpes simplex virus (HSV), human T-lymphotropic virus (HTLV) and parvovirus B19 [4]. In one study, 30 lymph node samples from KFD patients were tested against 12 controls for EBV. Cells positive for EBV-encoded RNA were discovered in necrotic regions of KFD-affected lymph nodes, raising the question of whether the condition could be a result of a hyperinflammatory immune reaction to EBV [5]. Another report demonstrated detection of EBV in the samples of all 10 patients with KFD, but EBV-encoded protein was found in only one patient [6]. There was also a significantly greater number of positive parvovirus B19 test results amongst the 33 lymph node samples compared to the 16 controls in a study conducted by Zhang, et al. [7]. Nonetheless, the evidence on this topic is conflicting, with several studies showing no relationship between viral infection and the development of KFD [4].

Autoimmune mechanisms have also been shown to potentially play a role in the pathogenesis of KFD. A study conducted by Sopeña, et al. detected autoimmune conditions, including SLE, thyroiditis, leukocytoclastic vasculitis and Sjogren's syndrome, in nine of the 20 patients diagnosed with KFD [8]. Out of these disorders the most commonly studied is SLE, with many reports describing KFD patients subsequently developing SLE or being diagnosed concurrently with the condition [4]. In addition to sharing similar sex and age distributions, the two conditions also have comparable lymphocytic and endothelial tubuloreticular structures histologically. However, further research is needed to elucidate a clear link.

On a molecular level, interferon-gamma and interleukin 6 (IL-6) have been demonstrated in the pathogenesis of KFD in a study of four men with the disease [9]. All four patients had elevated serum interferon gamma and IL-6 during the acute phase of KFD which subsequently returned to baseline during convalescence. Other proposed mechanisms include up-regulation of apoptosis-associated genes, such as caspase, and down-regulation of genes inhibiting apoptosis, including B-cell lymphoma 2 (BCL2) [10].

Clinical features

Lymphadenopathy is the most common clinical manifestation of KFD and occurs in 100% of patients. It typically involves the posterior cervical triangle though generalized lymphadenopathy can rarely be present [11]. The affected lymph nodes are usually tender, and their sizes vary from 0.5 to 4 cm. Fever is another primary symptom and is observed in 35% of patients. It is usually low-grade and persists for one week, though may be present for up to one month [12]. Other frequently described clinical features include rash (10%), fatigue (7%), arthritis (7%) and hepatosplenomegaly (3%). Less frequent symptoms such as weight loss, night sweats, sore throat, nausea and vomiting have been better observed in patients with extranodal disease [13]. The most common manifestation in those with extranodal disease is skin lesions including papules, plaques, nodules and facial malar erythema, which may be present in up to 40% of patients [14].

Investigations and diagnosis

Patients with KFD typically have normal blood counts though leukopenia, as seen in our patient, has been found to occur in up to 50% of cases. Atypical lymphocytes have also been noted in 25% of patients on peripheral blood film [15]. Other laboratory findings include elevated serum ESR, lactate dehydrogenase and mildly deranged liver function tests [16,17].

The diagnosis of KFD is made on lymph node biopsy. All patients are recommended to undergo a biopsy to confirm the diagnosis and to exclude more sinister conditions such as lymphoma. Excisional biopsy is considered the gold standard and is preferred over ultrasound-guided fine needle aspiration [3]. Typical histopathological findings include distortion of the nodal architecture due to irregular paracortical and cortical areas of coagulative necrosis as well as excessive karyorrhectic debris. Other features include an abundance of histiocytes and CD8-positive T cells and an absence of neutrophils [18].

Treatment and prognosis

Minimal guidance exists for the treatment of KFD with recommendations being based on either expert opinion or case reports. Observation is perhaps the most common and appropriate management strategy for patients with KFD given the self-limited nature of the condition [4]. Clinical features typically resolve spontaneously within one to four months [19]. Nonsteroidal anti-inflammatory drugs are often used as symptomatic therapy for fever and lymph node tenderness. Patients who have severe symptoms or extranodal manifestations such as KFD affecting the central nervous system, skin or eyes, have been treated with corticosteroids with good effect [4]. Some reports demonstrate successful treatment of recurrent KFD with hydroxychloroquine both as a monotherapy or in combination with corticosteroids [20], the latter of which was used for our patient. It is recommended that patients with KFD have regular follow-up for several years to monitor for the development of SLE and recurrences of KFD, the rate of which is observed to be anywhere from 4 to 15% [4].

Conclusion

KFD is an uncommon condition that mainly affects young Asian women and typically manifests as fever and cervical lymphadenopathy. Although it is often self-limiting, recognition is crucial so as to avoid the consequences of misdiagnosis and inappropriate treatment. As seen in the case of our patient, the clinical presentation can be variable and can often mimic other conditions such as SLE. Thus, clinicians should hold a high degree of suspicion of KFD for young women who have cervical lymphadenopathy, especially those of oriental origin.

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Statement of Equal Authors' Contribution

Cecilia drafted, edited and approved the manuscript as first author. Sherman provided Chinese medicine treatment to the patient, drafted and edited the manuscript.

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