

# Kikuchi-Fujimoto Disease Preceding Overlap Syndrome of Sjögren's Syndrome and Systemic Lupus Erythematosus: Literature Review Based on a Case Report

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## ABSTRACT

*Kikuchi-Fujimoto disease (KFD) is a benign, self-limiting histiocytic necrotizing lymphadenitis systemic disorder with unknown etiology. KFD has been known for half a century, but difficulties in distinguishing it remain. Its diagnostic significance is related to the increasing prevalence of KFD with autoimmune diseases in various timeframes. Systemic lupus erythematosus (SLE) is the most prevalent autoimmune connective tissue disease (AICTD) appearing alongside KFD. An 18-year-old female presented with acute muscle weakness, shortness of breath, fever, and significant weight loss for 5 months before admission. Pain and morning joint stiffness had been felt for 9 months. One year ago, she lumped her right neck and was diagnosed with KFD from the excision biopsy and immunohistochemical staining (CD68). Creatine-kinase enzymes and C-Reactive protein were elevated with a high anti-Ku and anti-Jo-1 negative level. There was a low level of complements, high anti-nuclear antibody titer, with positive anti-SS-A. Sialometry and Schirmer test showed reduced salivary and lacrimal gland production. We diagnosed this patient as having an overlap syndrome preceded by KFD. The AICTD involved was Sjögren's syndrome and SLE. Although KFD is considered a self-limiting disease, its occurrence should be noticed regarding the possibility of other autoimmune conditions. KFD usually coincides with AICTD, although it could also precede or occur afterward. This case is reported to raise awareness of the overlap syndrome preceded by KFD.*

**Keywords:** Kikuchi-Fujimoto disease, Overlap Syndrome, Sjögren's Syndrome, Systemic Lupus Erythematosus, Inflammatory Myositis.

## INTRODUCTION

Kikuchi-Fujimoto disease (KFD) has an unknown etiology.<sup>1,2</sup> There were difficulties in distinguishing KFD from other lymph node diseases.<sup>3</sup> The occurrence of KFD should increase our awareness since it could coincide (preceding, simultaneous, or after) with autoimmune diseases.<sup>4</sup> Systemic lupus erythematosus (SLE) is the most prevalent AICTD with KFD.<sup>5</sup> Still,

there are also other AICTDs such as Sjögren's syndrome (SjS), polymyositis, vasculitis, and other autoimmune diseases, such as thyroiditis, antiphospholipid syndrome, which have been reported with KFD.<sup>6-8</sup> Our patient had an overlap syndrome consisting of Sjögren's syndrome and SLE preceded by KFD. There is no specific treatment for KFD; corticosteroid treatment was necessary in only 16% of the cases; and

immunosuppressants have been recommended as an adjunct to corticosteroids in severe, life-threatening diseases.<sup>5</sup> However, there would be a huge therapeutic difference if AICTD is diagnosed in KFD patients. Thus, we reported this case to raise the awareness of AICTD preceded by KFD beyond SLE. The physicians should notice the occurrence of KFD regarding the possibility of autoimmune diseases that will lead to further investigation to obtain the right diagnosis and treatment.

### CASE ILLUSTRATION

An 18-year-old female was admitted to the hospital due to muscle weakness since three weeks before admission. She also complained about fever, cough, shortness of breath, swallowing difficulty, and weight loss (6 kg in the last 5 months). Nine months before, she began to feel dryness in her eyes and mouth, and pain on her wrists, elbows, and fingers accompanied with morning stiffness. In the four months before admission, she was prescribed 8 grams of methylprednisolone thrice daily. The patient has no other known comorbidities nor a similar family history.

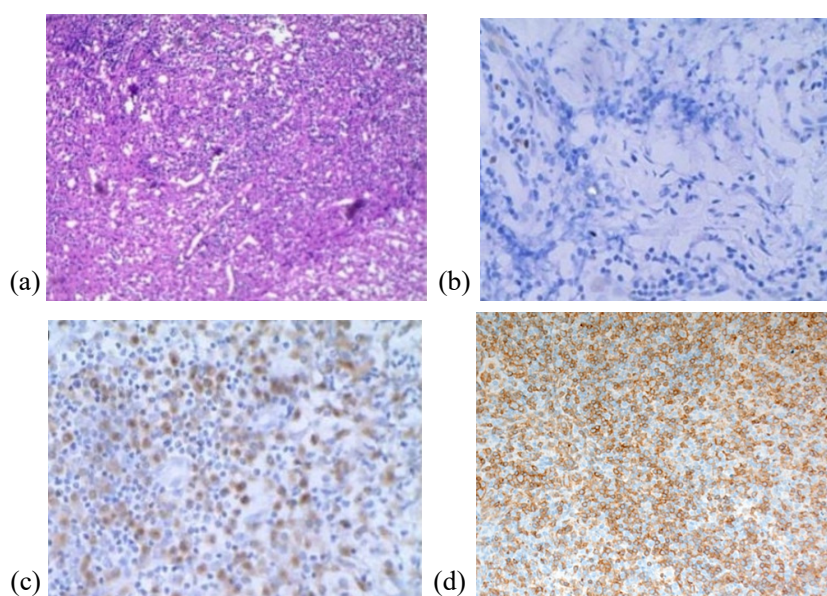
One year before admission, she had a painful lump on her right neck with no other symptoms, as seen in **Figure 1**. She underwent surgery and received no further treatment because it

was considered benign and self-limiting. The result of the biopsy followed by histologic and immunohistochemistry smear showed reactive chronic granulomatous lymphadenitis (non-neoplastic) lesion, positive for CD 3, CD 68, CD 10, and KI-67 supporting Kikuchi-Fujimoto disease (histiocytic necrotizing lymphadenitis) like seen in **Figure 2**.

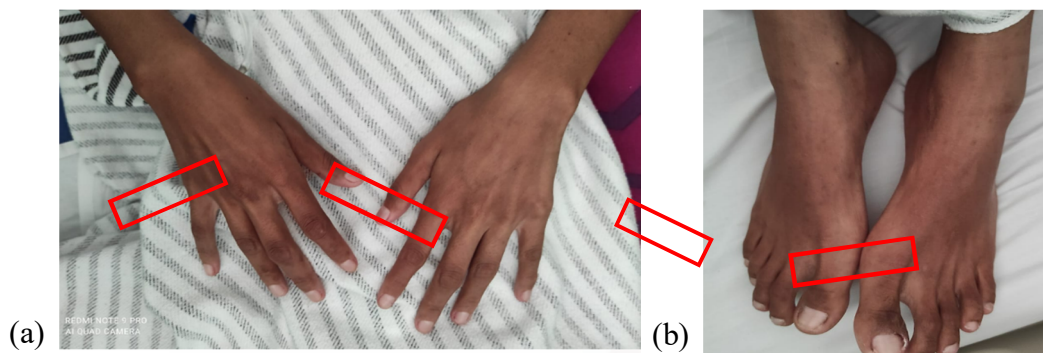
Our patient was underweight and had a motoric weakness (tetraparesis), especially on her proximal limbs (motoric examination of upper limbs 4433/3344 and lower limbs 4432/2344). There was tenderness in her metacarpophalangeal joints (MCP 2-4 bilateral) as seen in **Figure 3** and metatarsophalangeal joints (MTP 2-5 bilateral), right elbow joint,



**Figure 1.** Lump on the patient's right neck



**Figure 2.** Immunohistochemical staining of cervical lymph node demonstrating (a) hematoxylin-eosin staining (b) Ki67, (c) CD68 (adapted from Khan et al<sup>9</sup>), and (d) CD3 (adapted from Alshieban et al<sup>10</sup>)



**Figure 3.** Joint tenderness in (a) metacarpophalangeal and (b) metatarsophalangeal (b)

right shoulder joint, and both knees. Pain and hypertonus were felt in her upper quadrants and periumbilical abdomen area, without spasticity. Contracture and atrophy of upper and lower limb muscles can be seen in **Figure 4**.

Transaminase enzymes (Aspartate aminotransferase 103 U/L; Alanine aminotransferase 373 U/L), Lactate Dehydrogenase / LDH (1280 U/L), C-Reactive Protein (29.8 mg/L), Creatine-kinase (1970 U/L) were elevated with a high level of anti-Ku (167 U, strong positive). Electromyography and nerve velocity test examination found a myogenic lesion without overt myotonic and cramps. A muscle biopsy at her right hamstring muscle revealed fibrous tissue partly fibrotic and lipid, and no striated muscle was found. Blood complements (C3 and C4) were lower than normal (32 and 8 mg/dL), but anti-ds-DNA was within the normal limit (9.4 IU/ml). D-dimer was elevated (8700 ug/L), with Anti Cardiolipin antibody IgM positive in 2 examinations (12

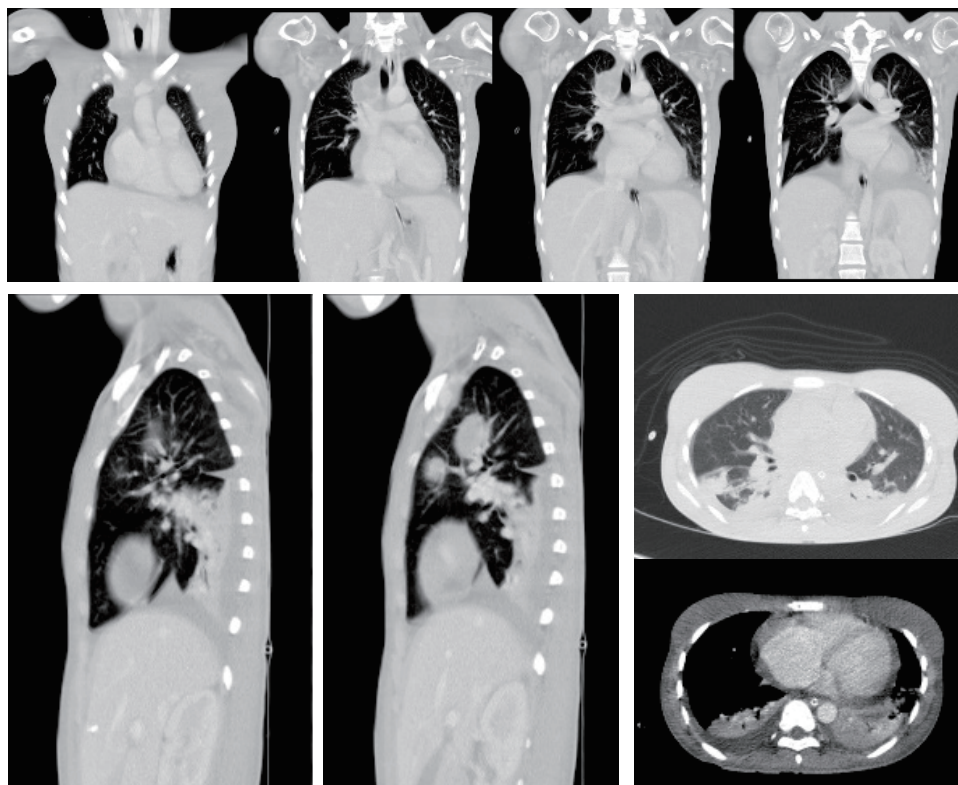
weeks interval), and Anti-nuclear antibody immunofluorescent (ANA IF) positive (>1/1000, nuclear membrane/rim pattern) with a positive result of anti-SS-A (++) and a borderline result of anti-ribosomal protein (+). She also had xerostomia (unstimulated salivary flow rate (USSFR) < 0.02 ml/min) and xerophthalmia (Schirmer test on her right eye 0 mm, left eye 2 mm).

Chest CT scan with IV-contrast showed multiple lymphadenopathies in the mediastinum (around 2.4 cm), bilateral pleural effusion, partial atelectasis at bilateral inferior lobes, minimal ground glass opacity, and consolidation at bilateral posterobasal, fibrosis at left lung (segment 5&9) and cardiomegaly accompanied with pericardial effusion as seen in **Figure 5**.

Echocardiography also confirmed mild pericardial effusion with normal ejection fraction. The fiberoptic evaluation of swallowing (FEES) result was moderate-severe neurogenic dysphagia at the pharyngeal phase with



**Figure 4.** Contracture and atrophy of (a) upper limb muscle and (b) lower limb muscle.



**Figure 5.** Chest CT Scan with IV contrast showed multiple lymphadenopathies in the mediastinum (around 2.4 cm), bilateral pleural effusion, partial atelectasis at bilateral inferior lobes, minimal ground glass opacity, and consolidation at bilateral posterodorsal, fibrosis at left lung (segment 5&9) and cardiomegaly accompanied with pericardial effusion

laryngopharyngeal reflux. She had a positive antiphospholipid antibody and a high probability of a thromboembolic event (Padua Score<sup>11</sup> 4).

We considered that inflammatory myositis, interstitial lung disease, dysphagia, and serositis in this patient were part of an overlap syndrome. Thus, we diagnosed this patient with an Overlap Syndrome (Sjögren's Syndrome and Systemic Lupus Erythematosus) preceded by Kikuchi-Fujimoto Disease. She was treated with 500 mg IV methylprednisolone on 3 consecutive days, 500 mg IV cyclophosphamide every 2 weeks (6 cycles), hydroxychloroquine 200 mg o.d., cotrimoxazole 960 mg o.d. on alternate days, and other symptomatic therapies including artificial tears and mouthwash. We also gave her clopidogrel 75 mg o.d oral and tapered the steroid dose to 35 mg (1 mg/kgBW) o.d oral prednisone for two weeks. Neurologists gave baclofen 10 mg b.i.d oral and she had a routine program for muscle strengthening, mobilization training, and orometer physiotherapy.

One month later, her condition gradually

improved, and was able to eat orally. Her joint and muscle pain had also resolved. After being treated with 6 doses of cyclophosphamide, her motoric became fully recovered in four extremities with Creatine-kinase level decreasing to 657 U/L, C-Reactive Protein 15 mg/L, and SLEDAI score 4 (low disease activity).

## DISCUSSION

Kikuchi-Fujimoto disease (KFD) was first reported in Japan in 1972 and manifested as cervical subacute necrotizing lymphadenitis.<sup>1,2</sup> This disease misdiagnosis rate is up to 40%.<sup>3</sup> KFD is characterized by regional lymphadenopathy with tenderness, predominantly in the cervical region, accompanied by mild fever and night sweats. Posterior cervical nodes are affected in about 80% of cases.<sup>12</sup> Fever (35%), fatigue (7%), joint pain (7%), erythematous rashes (10%), arthritis (5%), hepatosplenomegaly (3%), leucopenia (43%), high acute phase reactants (40%), and anemia (23%) are the most common findings.<sup>5</sup> Diagnostic laboratory and radiologic

test findings are nonspecific.<sup>13</sup> Predominantly 77% were female and 70% were younger than 30 years old.<sup>5</sup>

The cause of KFD is unknown and might be an exaggerated T cell-mediated immune response in genetically susceptible people to nonspecific stimuli. The incidence of DPA1\*01 and DPB1\*0202 alleles of HLA antigen LAHLA is significantly higher in patients with KFD than in healthy controls. These genes are extremely rare among Caucasians but relatively common among Asians. The tubular-reticular structures in the cytoplasm of stimulated lymphocytes and histiocytes have been seen in patients with KFD, which are described in endothelial cells and lymphocytes of patients with SLE and other autoimmune disorders.<sup>13</sup>

KFD is diagnosed based on an excisional biopsy of affected lymph nodes showing necrosis and karyorrhexis with paucity or absence of granulocytes.<sup>5,13</sup> The histiocytes express histiocyte-associated antigens, such as lysozyme, myeloperoxidase (MPO), and CD68.<sup>13</sup> This patient has had a typical clinical presentation of right single cervical lymphadenopathy proven by immunohistochemical staining showing histiocytic necrotizing lymphadenitis, reactive chronic granulomatous lymphadenitis (non-neoplastic) lesion, positive for CD 3, CD 68, CD 10, and KI-67 supporting Kikuchi-Fujimoto disease 1 year before muscle weakness and 7 months before other AICTD symptoms.

The differential diagnosis of KFD may include toxoplasmic lymphadenitis, infectious mononucleosis, cat-scratch disease, and Hodgkin's lymphoma.<sup>5</sup> Tuberculosis, plasmacytoid T-cell leukemia, Kawasaki disease, and myeloid tumor are also included in the differential diagnosis.<sup>14</sup> There is no specific treatment for KFD, and it mostly lasts 1 to 3 months, up to 1 year.<sup>3</sup> The disease was self-limiting in 156 cases (64%), and corticosteroid treatment was necessary in 16 cases (16%).<sup>5</sup> Nonsteroidal anti-inflammatory drugs (NSAIDs) may be used to alleviate lymph node tenderness and fever. Indications for corticosteroids include neurologic involvement, hepatic involvement, and severe lupus-like syndrome. Immunosuppressants can be used as an adjunct

to corticosteroids in severe disease. Intravenous immunoglobulin (IVIG) is chosen in a few cases of refractory KFD.<sup>13</sup> The mortality rate of KFD alone is 2.1%.<sup>5</sup>

KFD is not an independent condition and most likely develops due to an autoimmune mechanism.<sup>15,16</sup> The diagnosis of KFD can precede, postdate, or coincide with the diagnosis of SLE.<sup>13</sup> Zaccarelli et al. found out that autoimmune disease may be "preceding" (11 cases) "simultaneous" (20 cases) or "post" (8 cases) KFD. Also, the autoimmune disease can be present with a complete clinical picture or only with the presence of autoantibodies.<sup>4</sup> Sopena et al. followed 20 KFD patients and autoimmune diseases were detected in 9 women (53%): 2 patients with SLE before, 1 patient simultaneous, and 1 patient after KFD, 2 patients developed primary SjS after KFD, 1 thyroiditis before KFD, 1 SLE-like, and 1 antiphospholipid antibodies after KFD. Leukocytoclastic vasculitis was found in 2 patients; one of them eventually developed SLE. In females, painful adenopathies, and cytopenias are significantly associated with autoimmune diseases.<sup>8</sup> There was a case reported by Radfar et al. of a patient with KFD who developed SjS 8 years after diagnosis of KFD.<sup>6</sup> There is also a report from China of two patients, a 14-year-old boy with SLE and secondary SjS, and a 9-year-old boy with primary SjS who was diagnosed after 3 years of disease duration. Both had KFD.<sup>6,17</sup> Jun et al. have also found 7 case reports in which KFD and SjS were diagnosed simultaneously in 1 patient, KFD preceding SjS (312 months latency) in 1 patient, and KFD after SjS (2-120 months latency) in 5 patients.<sup>18</sup> We found only one case of KFD and PM reported by Wilkinson and Nichol of a 41-year-old Indian woman diagnosed with KFD who subsequently developed polymyositis with pulmonary involvement.<sup>7</sup> There are two cases of KFD preceding Mixed Connective Tissue Disease (MCTD) reported by Cheng et al. and Ogata et al.<sup>15,19</sup>

We found a case report of an overlap syndrome (RA and SLE) that concurred with KFD, reported by Campbell et al.<sup>21</sup> We report a case of KFD preceding overlap syndrome that consists of Sjögren's Syndrome, SLE, and

inflammatory myositis.

When the patient was admitted to our hospital, she had tetraparesis especially on her proximal limbs, accompanied by pain and hypertonus on her upper quadrants and periumbilical area of the abdomen, without spasticity. Stiff-person syndrome (SPS), characterized by progressive rigidity and muscle spasms affecting the axial and limb muscles, has been ruled out by neurologists. Most patients with SPS have antibodies directed against the glutamic acid decarboxylase.<sup>21</sup> The patient was checked for that antibody and was negative (<5 IU/mL). Electromyography and nerve velocity test examination were conducted, supporting inflammatory myositis that did not fulfill the criteria for Polymyositis (Anti-Jo-1 negative, EULAR/ACR classification criteria for IIM 2017 score 4.4).<sup>22,23</sup> Idiopathic inflammatory myopathy (IIM) is the umbrella term that includes dermatomyositis (DM), polymyositis (PM), overlap myositis (OM), inclusion body myositis (IBM), and necrotizing autoimmune myopathy (NAM), also known as immune-mediated necrotizing myopathy.<sup>24</sup> PM and DM are relatively rare (<10 per 100,000 individuals).<sup>25</sup> An analysis of six large cohorts showed that 6.5-36.7 % of IIM presented as overlap syndrome (OS).<sup>26</sup> Patients with myositis overlap syndrome are almost always responsive to steroids.<sup>25</sup> Regarding the high level of anti-Ku in our patient, Sifuentes Giraldo et al. found out that Anti-Ku Antibodies are more common in overlap syndromes especially when myositis is present, and are associated with severe and corticosteroid-resistant ILD.<sup>23</sup>

This patient had Sjögren's syndrome (SjS) (ACR/EULAR 2016 classification criteria for Primary Sjögren's syndrome score 5).<sup>26</sup> Sjögren's syndrome (SjS) is a systemic autoimmune disease with antinuclear antibodies that are frequently detected (specifically anti-Ro/SS-A) and hypocomplementaemia. The symptoms are dominated by sicca syndrome caused by immune-mediated glandular involvement, accompanied by fatigue, musculoskeletal pain, and systemic features, complicated by lymphoma in 2-5% of patients.<sup>26</sup> The ACR/EULAR 2016 classification criteria for Primary SjS were fulfilled/scored 5 (Anti-SS-A positive,

xerostomia, and xerophthalmia) in this patient.<sup>12</sup> The management is symptomatic treatment and broad-spectrum immunosuppression.<sup>26</sup>

The differentiation of KFD from SLE can be problematic because both can show similar clinical features.<sup>27</sup> In KFD, although there may be a decrease in C4, the RF and ANA studies are generally negative.<sup>14</sup> She had a history of fever, arthritis, serositis, ANA IF positive, and hypocomplementemia (ACR/EULAR 2019 SLE classification criteria scored 20).<sup>28</sup> SLE and SjS are related clinically and serologically. Anti-Ro (anti-SS-A) and anti-La (anti-SS-B) are found in both diseases.<sup>6</sup> Anti-U1RNP in this case was negative; and Systemic lupus erythematosus (SLEDAI 19, ACR/EULAR 2019 SLE classification criteria score 20).<sup>28</sup> Thus, she was diagnosed as OS with SjS and SLE as the AICTD involved. Inflammatory myositis, interstitial lung disease, dysphagia, and serositis also existed in this case as part of the overlap syndrome. The concept of OS implies the occurrence of two or more well-defined AICTDs in the same patient.<sup>29</sup> Patients may be presented with evidence of more than one disease simultaneously or they may develop different diseases sequentially.<sup>26</sup> OS is not frequent, and its descriptions in the literature are limited to a few case reports.<sup>29</sup> The management was based on its clinical features.<sup>25</sup>

The treatment of our case was aimed at severe SLE (serositis), inflammatory myositis, and interstitial lung disease; hence, we gave cyclophosphamide and a pulse dose of steroids, accompanied by symptomatic treatments.<sup>30</sup> We also have a special caution about the high risk of a thromboembolic event (immobilization state, high d-dimer, prolongation of aPTT, Padua score 4) and antiphospholipid antibody positive (in 2 examinations with a 12-week interval). Thus, we gave a prophylactic dose of unfractionated heparin and then switched to clopidogrel when discharged.

## CONCLUSION

KFD is a self-limiting disease whose occurrence should get special attention regarding the possibility of autoimmune conditions. Individuals with KFD should be examined

systemically, and they must be under regular follow-up to monitor the manifestations of AICTD. Although KFD usually co-occurs with AICTD, it could also occur before or after it. Systemic lupus erythematosus (SLE) is the most common AICTD found with KFD. This case is reported to raise the awareness of AICTD associated with KFD beyond SLE.

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