



Reumatismo - The Italian Journal of Rheumatology

<https://www.reumatismo.org/reuma>

eISSN 2240-2683

Publisher's Disclaimer. E-publishing ahead of print is increasingly important for the rapid dissemination of science. The Early Access service lets users access peer-reviewed articles well before print/regular issue publication, significantly reducing the time it takes for critical findings to reach the research community.

These articles are searchable and citable by their DOI (Digital Object Identifier).

Reumatismo is, therefore, E-publishing PDF files of an early version of manuscripts that have undergone a regular peer review and have been accepted for publication, but have not been through the copyediting, typesetting, pagination, and proofreading processes, which may lead to differences between this version and the final one.

The final version of the manuscript will then appear in a regular issue of the journal.

The E-publishing of this PDF file has been approved by the authors.

Please cite this article as:

Coccia C, Lepri G, Levani J, et al. **Rare in the rare: Kikuchi-Fujimoto disease associated with connective tissue disorders. A report of our experience.** *Reumatismo* doi: 10.4081/reumatismo.2025.1853

Submitted: 31-01-2025

Accepted: 09-06-2025

 © the Author(s), 2025
Licensee PAGEPress, Italy

Note: The publisher is not responsible for the content or functionality of any supporting information supplied by the authors. Any queries should be directed to the corresponding author for the article.

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article or claim that may be made by its manufacturer is not guaranteed or endorsed by the publisher.

**Rare in the rare: Kikuchi-Fujimoto disease associated with connective tissue disorders.
A report of our experience**

Carmela Coccia, Gemma Lepri, Juella Levani, Silvia Bellando Randone, Serena Guiducci

Division of Rheumatology, Department of Experimental and Clinical Medicine, AOU Careggi,
University of Florence, Italy

Correspondence: Carmela Coccia, Division of Rheumatology, Department of Experimental and Clinical Medicine, AOU Careggi, University of Florence, 50134, Florence, Italy.

E-mail: carmen.coccia@gmail.com

Key words: Kikuchi-Fujimoto disease, lymphadenopathy, systemic lupus erythematosus, Sjögren's syndrome, connective tissue diseases.

Contributions: all the authors made a substantial intellectual contribution. CC, conceived the manuscript and participated in the draft of the manuscript; GL, participated in the draft of the manuscript and in its revision; JL, SBR, reviewed the manuscript; SG, reviewed the draft and the manuscript.

Conflict of interest: the authors declare no conflict of interest.

Ethics approval and consent to participate: not applicable.

Patient consent for publication: written informed consent was obtained.

Availability of data and materials: all data underlying the findings are fully available.

Funding: none.

Summary

Kikuchi-Fujimoto disease (KFD) is a rare and benign lymphadenopathy of unknown etiology. Usually, it is an isolated and self-limiting condition requiring no specific therapy; however, in some cases, it may be associated with an autoimmune disease.

Here, we report three cases of KFD developing an associated autoimmune connective disorder: the first case presented with Sjögren's syndrome, and the other two had a diagnosis of systemic lupus erythematosus.

Introduction

Kikuchi-Fujimoto disease (KFD) is a rare, benign, and self-limiting form of lymphadenopathy of unknown etiology. It typically presents with a single cervical lymphadenopathy, often accompanied by systemic symptoms, and it is more common in young adult females (1). The diagnosis of KFD is based on histopathological analysis, and its etiopathogenesis remains uncertain, probably resulting from an abnormal T-cell-mediated immune response reaction to environmental triggers, such as viral infections. Considering the rare but possible association of KFD with autoimmune diseases, another hypothesis suggests a possible role of autoimmune processes (1, 2).

Here, we describe the case of a patient with KFD who subsequently developed Sjögren's syndrome (pSS), and two cases of KFD associated with systemic lupus erythematosus (SLE) (Table 1).

Case Report 1

A 28-year-old female with a history of autoimmune thyroiditis presented with 1-month lateral cervical lymphadenopathy associated with asthenia and evening fever (max 37.7°C). The physical examination did not reveal hepatosplenomegaly, skin lesions, or signs of arthritis. Laboratory investigations showed normal erythrocyte sedimentation rate (ESR) and C-reactive protein values and absence of antinuclear antibodies (ANA). Serologies for hepatitis B virus (HBV), hepatitis C virus (HCV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), human immunodeficiency virus (HIV), and tuberculosis tests were negative. To exclude neoplastic hematologic disease, lymph node excisional biopsy was performed, and the histopathological examination revealed a histiocytic necrotizing lymphadenitis compatible with KFD. The symptomatology regressed spontaneously within 2 months. However, after 15 months, the patient started to complain of intense asthenia and severe xerostomia and xerophthalmia. The physical examination revealed multiple bilateral cervical lymphadenopathies with benign ultrasound features, and the repetition of immunological tests revealed ANA (1:320, homogeneous pattern) and anti-Ro/SSA antibodies positivity. Schirmer's test was abnormal (<5 mm bilaterally/5 minutes), and minor salivary gland biopsy showed a focal lymphocytic sialadenitis with score 3 using Chisholm's criteria (3). The diagnosis of pSS was established according to the European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) 2016 criteria, and therapy with hydroxychloroquine (200 mg/day) was started with improvement in asthenia and cervical lymphadenopathies.

Case Report 2

A 27-year-old girl with a previous episode of spontaneous pneumothorax was seen for an 1-month history of an isolated lateral cervical lymphadenopathy without systemic symptoms. HBV, HCV, HIV, EBV, CMV, *Borrelia burgdorferi*, and tuberculosis tests were negative. The lymph node biopsy showed multiple necrotic areas consisting of deposits of fibrin and nuclear debris surrounded by collections of histiocytes with small-sized T lymphocytes (predominantly CD8+), supporting the diagnosis of a KFD necrotizing lymphadenitis. Laboratory tests highlighted positivity for ANA (1:640, homogeneous pattern) and for anti-double-stranded DNA (anti-dsDNA); in addition, lupus anticoagulant (LAC) was present. The patient reported moderate and persistent chest pain, the cardiological evaluation was negative, and chest computed tomography (CT) revealed a mild pericardial effusion and bilateral axillary subcentimetric lymph nodes. According to EULAR/ACR 2019 criteria, the patient was classified as SLE, and therapy with hydroxychloroquine (200 mg/day) was started. After 6 months, the disease activity was in good control, and the lateral cervical lymphadenopathy was significantly reduced.

Case Report 3

A 57-year-old woman with no relevant previous diseases or family history of autoimmune diseases, was referred to our clinic because of a 2-month history of intermittent fever (max 37.5°C), episodes of night sweats, and asthenia. The physical examination revealed a lateral cervical lymphadenopathy. Infectious disease tests were negative, and a lymph node biopsy was performed to exclude lymphoma,

with histological findings of histiocytic lymphadenitis compatible with KFD. For the persistence of constitutional symptoms, hydroxychloroquine (200 mg/day) and low-dose prednisone (5 mg/day) were prescribed with an initial good clinical response. However, after 2 months, she presented an exacerbation of systemic symptoms, and a total-body positron emission tomography with fluorine-18-fluorodeoxyglucose showed axillaries, para-aortic, peri-aortic, iliac-femoral, and inguinal lymphadenopathies. The patient also reported inflammatory arthralgias and Raynaud's phenomenon. Blood tests showed lymphopenia (lymphocytes 370/mm³), elevation of ESR (70 mm/h), and reduction of C4 complement (5.3 mg/dL with normal range 10-40 mg/dL). Immunological examinations showed positivity for ANA (1:1280, homogeneous pattern), anti-dsDNA, anti-ribonucleoprotein antibodies, anti-nucleosome and anti-ribosomal P protein antibodies, and the presence of LAC. The patient was diagnosed as SLE according to the EULAR/ACR 2019 criteria, and a few months later, a chest CT showed interstitial lung disease (ILD) findings compatible with a non-specific interstitial pneumonia pattern. Pulmonary function tests (PFTs) confirmed a restrictive pattern (forced vital capacity of 80%predicted, 1 sec-forced expiratory volume of 79% predicted, and a diffusing capacity for carbon monoxide of 54% predicted). Considering joint, lung inflammatory involvement, and the persistence of multiple lymphadenopathies, immunosuppressive therapy with rituximab was started (1000 mg on days 1 and 15 every 6 months) with good tolerance. The 12-month follow-up visit revealed stability in respiratory symptoms and PFTs and a complete resolution of systemic symptoms and inflammatory arthralgias.

Discussion

KFD, also known as subacute necrotizing histiocytic lymphadenitis, is a rare, benign, and generally self-limiting disease, clinically characterized by lymphadenopathy and fever. It has been reported especially in young adult females, and in all ethnic groups (1). Although its etiopathogenesis is unclear, clinicopathologic features are suggestive of a T-cell and histiocyte-mediated immune response to an infectious factor or an autoimmune mechanism (4). Numerous viruses have been proposed as possible etiologic factors leading to an intense inflammatory reaction, and among them, EBV, herpes simplex virus, varicella zoster virus, and human herpes viruses are the most frequently reported (4, 5). The autoimmune hypothesis is supported by the observation that KFD may be associated with autoimmune diseases, most frequently with SLE (2, 4). Although the relationship between KFD and SLE remains unknown, some authors have suggested that KFD may be an incomplete phase of lupus lymphadenitis. However, the difference in histological findings between the two diseases seems to deny this hypothesis (6); particularly, the presence of hematoxylin bodies (collections of nuclear DNA) and DNA deposits in vessel walls is characteristic of SLE lymphadenitis and not observed in KFD (7).

In addition to SLE, KFD has been reported in association with other autoimmune conditions such as pSS, mixed connective tissue disease, polymyositis, scleroderma, Still's disease, autoimmune thyroiditis, and autoimmune hepatitis (1, 2, 8, 9). Recently, some cases of associations between KFD and COVID-19 infection or vaccination have also been described (10, 11).

Clinically, the KFD onset may be sub-acute or acute, and the most common symptoms and signs are represented by cervical lymphadenopathy with tenderness, intermittent and low-grade fever, and night sweats. Less frequently, patients may complain of skin rash, arthralgia, asthenia, and hepatosplenomegaly (1), and, more rarely, the disease may present as generalized lymphadenopathy (12). KFD can mimic numerous infectious lymphadenitis (especially viral and tubercular infections) and autoimmune lymphadenopathy. Furthermore, a differential diagnosis with malignant hematological conditions, especially non-Hodgkin lymphoma, is mandatory. In this context, excisional lymph node biopsy is essential for a correct diagnosis of KFD. Histological findings usually reveal a partially preserved lymph node architecture with follicular hyperplasia, expansion of the paracortex with well-circumscribed areas of patchy necrosis. Occasionally, only isolated apoptotic cells, scattered in large sheets of histiocytes and mixed with cellular debris, are present. Necrotic foci,

so-called growing histiocytes, are common. Small lymphocytes, activated T cells, and some plasma cells are present and scattered among histiocytes (5).

As mentioned above, KFD is generally a benign and self-limiting condition, and symptoms frequently resolve in a few months. There are no treatment guidelines for KFD, and recommendations are based on case reports and expert opinions. Although it often does not require specific treatment, patients with persistent symptoms can be treated with antipyretic, anti-inflammatory drugs, steroids, and/or hydroxychloroquine in more severe cases (8).

All three of our cases involved female patients with cervical lymphadenopathy, as typically reported in the literature. In all patients, the initial clinical suspicion was lymphoma, with which KFD is often misdiagnosed (12); for this reason, in all patients, an excisional lymph node biopsy was performed. Our experience agrees with other clinical reports reported in the literature and describing KFD occurrence in the context of a connective tissue disease (CTD). Table 2 reports the most relevant cases of KFD associated with SLE or pSS published in the last 5 years, and SLE results to be more frequent than pSS in KFD patients (6,13-20). In most of these cases, diagnosis of SLE or pSS was performed at the same time as KFD onset, and in rare cases, an autoimmune condition was already present (Table 2). Interestingly, our first patient developed pSS after 15 months from KFD diagnosis, suggesting the possibility that KFD patients may present CTD also during the follow-up. According to already published cases, our second KFD patient only presented an isolated cervical lymphadenopathy without systemic symptoms, and immunological investigations revealed an underlying subclinical form of SLE. Conversely, the third KFD case was associated with persistent and important systemic symptoms and with a severe form of SLE, complicated by generalized lymphadenopathy and pulmonary involvement.

Considering the paucity of clinical trials focused on the treatment of ILD in SLE patients, the current therapeutic recommendations are based on small case series, case reports, physicians' experience, and results from studies on ILD in other autoimmune diseases (21). According to our clinical experience, we decided to treat the patient with rituximab with a good clinical response.

Conclusions

KFD is a rare lymphadenopathy of unknown etiology. It can mimic many other conditions, and an accurate differential diagnosis is mandatory. KFD diagnosis is primarily histological, and a lymph node biopsy is necessary for its confirmation. While in most cases KFD is an isolated, benign, and self-limiting condition requiring no specific therapy, clinicians should be aware that sometimes it can precede or coexist with an autoimmune disorder. Therefore, immunological investigation and an accurate long-term follow-up are encouraged in patients with a diagnosis of KFD to identify an underlying autoimmune disease early.

References

1. Ahmed Z, Quadir H, Hakobyan K, Gaddam M, Kannan A, Ojinnaka U, et al. Kikuchi-Fujimoto disease: a rare cause of cervical lymphadenopathy. *Cureus* 2021; 13: e17021.
2. Zaccarelli F, de Vincentiis M, D'Erme G, Greco A, Natalucci F, Fusconi M. Kikuchi-Fujimoto disease: a distinct pathological entity but also an "overlap" autoimmune syndrome: a systematic review. *Curr Rheumatol Rev* 2023; 19: 159-67.
3. Chisholm DM, Mason DK. Labial salivary gland biopsy in Sjögren's disease. *J Clin Pathol* 1968; 21: 656-60.
4. Perry AM, Choi SM. Kikuchi-Fujimoto disease: a review. *Arch Pathol Lab Med* 2018; 142: 1341-6.
5. Rosado FGN, Tang YW, Hasserjian RP, McClain CM, Wang B, Mosse CA. Kikuchi-Fujimoto lymphadenitis: role of parvovirus B-19, Epstein-Barr virus, human herpesvirus 6, and human herpesvirus 8. *Hum Pathol* 2013; 44: 255-9.
6. Aun JA, Hubbard MJ. Kikuchi-Fujimoto disease heralding systemic lupus erythematosus. *J Am Osteopath Assoc* 2020; 120: 934-9.

7. Masab M, Surmachevska N, Farooq H. Kikuchi-Fujimoto Disease. Treasure Island, FL, USA: StatPearls Publishing; 2025.
8. Dumas G, Prendki V, Haroche J, Amoura Z, Cacoub P, Galicier L, et al. Kikuchi-fujimoto disease: Retrospective study of 91 cases and review of the literature. *Medicine* 2014; 93: 372-82.
9. Cadório MJ, Oliveira J, Gama J, Duarte C. Kikuchi-Fujimoto disease and primary Sjögren's syndrome coexisting: a case-based literature review. *Mod Rheumatol Case Rep* 2025; 9: 110-6.
10. Graef A, Willett A, Dang AH, Balakrishna J, Nicely C, Baiocchi R. A case report: Kikuchi disease associated with a positive auto-immune panel triggered by COVID-19 infection. *Cureus* 2023; 15: e50911.
11. Masiak A, Lass A, Kowalski J, Hajduk A, Zdrojewski Z. Self-limiting COVID-19-associated Kikuchi-Fujimoto disease with heart involvement: case-based review. *Rheumatol Int* 2022; 42: 341-8.
12. Deaver D, Horna P, Cualing H, Sokol L. Pathogenesis, diagnosis, and management of Kikuchi-Fujimoto disease. *Cancer Control* 2014; 21: 313-21.
13. Yousefi M, Rukerd MRZ, Binafar H, Shoaie S, Mirkamali H, Pourzand P, Kaveh R. The co-occurrence of Kikuchi-Fujimoto disease and systemic lupus erythematosus: a case report. *J Med Case Rep* 2023; 17: 448.
14. Rana MBM, Fatima M, Rana IM, Haseeb Ul Rasool M, Abosheaishaa H, Abrudescu A, Bandagi S. Kikuchi-Fujimoto disease with systemic lupus erythematosus and systemic sclerosis overlap: a unique clinical presentation. *Cureus* 2023; 15: e44986.
15. Hurtado-Díaz J, Espinoza-Sánchez ML, Rojas-Milán E, Cimé-Aké E, de Los Ángeles Macias M, Romero-Ibarra L, Vera-Lastra OL. Kikuchi-Fujimoto disease: report of a case with progression to lupus nephritis. *Am J Case Rep* 2021; 22: e927351.
16. Cindy C, Wibowo SAK, Ariane A, Hidayat R. Kikuchi-Fujimoto disease preceding overlap syndrome of Sjögren's syndrome and systemic lupus erythematosus: literature review based on a case report. *Acta Med Indones* 2024; 56: 210-7.
17. Wiśniewska K, Pawlak-Buś K, Leszczyński P. Kikuchi-Fujimoto disease associated with primary Sjögren's syndrome - literature review based on a case report. *Reumatologia* 2020; 58: 251-6.
18. Gouda W, Alsaqabi F, Almurshed M, Mostafa AA, Albasri A, Negm A, et al. Kikuchi-Fujimoto disease, simultaneously diagnosed with systemic lupus erythematosus in an Arabic female: an agonizing combination. *J Int Med Res* 2024; 52: 3000605241248884.
19. Pham AK, Castillo SA, Barton DT, Rigby WF, Guill MA, Lucas R, LeBlanc RE. Kikuchi-Fujimoto disease preceded by lupus erythematosus panniculitis: do these findings together herald the onset of systemic lupus erythematosus? *Dermatol Online J* 2020; 26: 13030/qt6tx957m2.
20. Pradhan S, Sirka CS, Dash G, Sahu K, Rout AN. A challenging case of Kikuchi-Fujimoto disease with systemic lupus erythematosus complicated with hemophagocytic lymphohistiocytosis in a young man. *Indian J Dermatol Venereol Leprol* 2021; 87: 78-82.
21. Amarnani R, Yeoh SA, Denny EK, Wincup C. Lupus and the lungs: the assessment and management of pulmonary manifestations of systemic lupus erythematosus. *Front Med* 2020; 7: 610257.

Table 1. Summary of the principal characteristics of our three patients.

Case	Age	Gender	KFD clinical presentation	Latency (months)	CTD type	Autoantibodies	Therapy
1	28	female	lateral cervical lymphadenopathy, fever, asthenia	15 (before)	pSS	ANA (1:320) anti-Ro/SSA	HCQ (200 mg/day)
2	27	female	isolated lateral cervical lymphadenopathy	0 (coexist)	SLE	ANA (1:640) anti-dsDNA LAC anti-B2GP1	HCQ (200 mg/day)
3	57	female	lateral cervical lymphadenopathy, fever, night sweats, asthenia	2 (before)	SLE	ANA (1:1280) anti-dsDNA anti-RNP, anti-nucleosomes anti-ribo P	HCQ (200mg/day) RTX (1000 mg on days 1 and 15)

ANA, antinuclear antibody; anti-B2GP1, anti- β -2-glycoprotein; anti-dsDNA, anti-double-stranded DNA; anti-ribo P, anti-ribosomal P protein; anti-RNP, anti-ribonucleoprotein; CTD, connective tissue disease; HCQ, hydroxychloroquine; KFD, Kikuchi-Fujimoto disease; RTX, rituximab; SLE, systemic lupus erythematosus; pSS, Sjögren's syndrome.

Table 2. Summary of case reports of Kikuchi-Fujimoto disease associated with systemic lupus erythematosus or Sjögren's syndrome published within the last 5 years.

Reference	Gender	Medical history	Presence of autoimmune laboratory abnormalities (at onset of KFD symptoms/signs)	Initial diagnostic suspicion	Treatment at KFD diagnosis	Follow-up	Diagnosis of an associated autoimmune disease
Yousefi <i>et al.</i> (13)	female		ANA and anti-dsDNA positivity	SLE	Hydroxychloroquine, corticosteroids	Benefit (2 and 6 months of follow-up)	SLE
Rana <i>et al.</i> (14)	female	SLE-SSc overlap syndrome, G6PD deficiency	low C3 levels, anti-DNA, anti-SSA Ro and anti-topo I positivity		Mycophenolic acid, corticosteroids		KFD in patient with SLE-SSc overlap
Hurtado-Díaz <i>et al.</i> (15)	female		ANA positivity, and anti-dsDNA positivity, low C3 levels, low C4 levels	Hematologic malignancies	Paracetamol, naproxen, cyclophosphamide, mycophenolic acid, hydroxychloroquine	Benefit (2 years follow-up)	SLE
Cindy <i>et al.</i> (16)	female		ANA positivity, anti SSA positivity, low C3 levels, low C4 levels	Hematologic malignancies	None		SLE/pSS overlap
Aun <i>et al.</i> (6)	female		ANA positivity, anti-Smith positivity, anti-ribonucleoprotein positivity		Colchicine, hydroxychloroquine, corticosteroids	Benefit (6 months follow-up)	SLE
Wiśniewska <i>et al.</i> (17)	female	Hypothyroidism	ANA positivity, anti-SSA/Ro positivity	Infectious disease	Corticosteroids, hydroxychloroquine, methotrexate		pSS
Gouda <i>et al.</i> (18)	female		ANA positivity, anti-dsDNA positivity	Infectious disease	Corticosteroids, hydroxychloroquine, cyclosporine A, Belimumab	Benefit (6 months follow-up)	SLE
Pham <i>et al.</i> (19)	female		ANA positivity, anti-dsDNA positivity	Hematologic malignancies	None		SLE
Pradhan <i>et al.</i> (20)	male		ANA positivity, anti-dsDNA positivity		Corticosteroids, hydroxychloroquine	Benefit (22 weeks follow-up)	SLE

ANA, antinuclear antibody; KFD, Kikuchi-Fujimoto disease; pSS, Sjögren syndrome; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.