

## Kikuchi Fujimoto's Disease: A Strange Cause of Cervical Lymphadenopathy, As A Differential Diagnosis of Nodal Tuberculosis: A Case Report in A Public Hospital - Peru

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**Received:** 27 January 2023; **Accepted:** 20 March 2023

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### ABSTRACT

Kikuchi-Fujimoto disease is a rare cause of lymphadenopathy of unknown etiology to date. Its clinical manifestations are the presence of lymphadenopathies associated with fever, diaphoresis, and night sweats. The diagnosis is made by histopathology and the exclusion of other pathologies, and its management is symptomatic. A case is reported of a 26-year-old woman from Venezuela, from the district of San Juan de Miraflores, department of Lima - Peru, who presented with an increase in the volume of the cervical lymph node in 3 months, very painful associated with night sweats. The diagnosis was established by the anamnesis, clinical picture, laboratory tests, and pathological anatomy; she received symptomatic treatment with a favorable evolution. The clinical, laboratory, and therapeutic aspects of the disease are discussed.

**Keywords:** Kikuchi-Fujimoto Disease, Lymphadenopathy, Necrotizing Lymphadenitis

### Introduction

Histiocytic necrotizing lymphadenitis, which is traditionally known as Kikuchi-Fujimoto disease (KFD), is of rare and unknown cause, but it debuts with cervical lymphadenopathy that is frequent in populations of adult and pediatric age groups (Singh and Shermetaro, 2019). There were reports of this pathology in Japan for the first time in 1972 (Singh and Shermetaro, 2019), since when it has been reported worldwide, but more frequently in the Asian continent. In Peru, it was reported for the first time in 2017 (Chung Ching, 2017).

It usually affects young adults (under 40 years old) but can occur in any age group. Most reports show a female predominance; however, some studies from Asian countries suggest that the proportion between men and women is closer to 1:1 (Perry and Choi, 2018). While it is true the etiology of KFD is not well identified, but they have been associated with viral pathologies, including herpes simplex virus (HSV), varicella-zoster (VZV) infection, and Epstein-Barr virus (EBV). as well as autoimmune pathologies and as a major representative the disease systemic lupus erythematosus (SLE) and Sjogren's syndrome have been observed (Ahmed *et al.*, 2021).

KFD typically follows a benign course, with resolution of lymphadenopathy within the following six months (Singh and Shermetaro, 2019).

The list of differential diagnoses of Kikuchi-Fujimoto's disease is extensive. Among the main ones in our setting include primarily ganglionic tuberculosis, in addition to others such as lymphoma, systemic lupus erythematosus, infectious mononucleosis, toxoplasmosis, HIV, Bartonella henselae, Kawasaki disease, sarcoidosis, herpes simplex and syphilis (Córdova-Pluma *et al.*, 2017).

The only way to establish the diagnosis is by performing lymph node biopsy and histopathological findings, characterized by coagulative necrosis with abundant remnants of karyorrhexis in paracortical areas (Córdova-Pluma *et al.*, 2017).

## Case Report

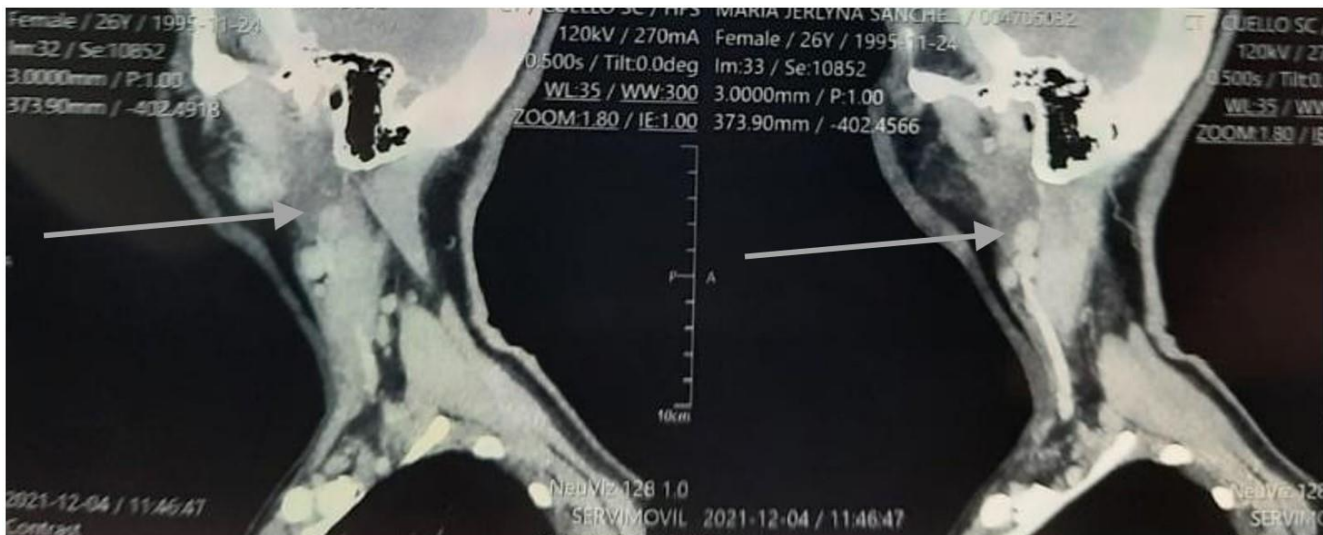
A case report is presented of a 26-year-old woman, a native of Venezuela and resident of the district of San Juan de Miraflores, department of Lima, Peru. The patient has lived in Peru for four years and is a dental technician, single, with no children. She denies any history of chronic diseases, family history of importance, or raising animals. Her last trip was to the department of Piura in January 2021.

The patient reports a period of illness of approximately three months, with the presence of enlarged cervical lymph nodes, with insidious onset and progressive course up to a maximum size of 10 cm in diameter, located in the left cervical region, indurated, mobile and painful (Fig. 1); associated with episodes of night sweats. She denies fever, nausea/vomiting, or weight loss.

The patient attended a medical consultation where a cervical CT scan and a lymph node biopsy were performed after clinical examination, laboratory tests, smear microscopy, culture, and Xpert for tuberculosis in sputum. The CT scan revealed multiple bilateral cervical adenopathies, the largest of 10mm (Fig. 2).



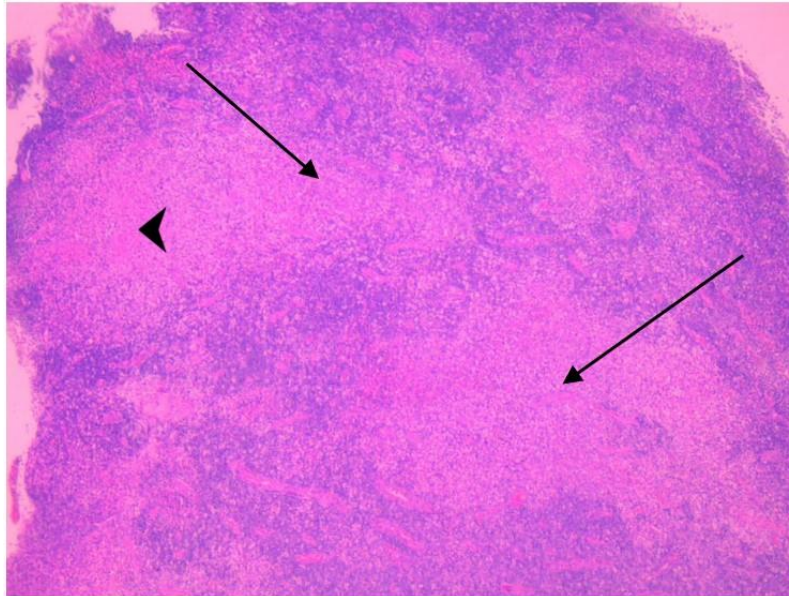
**Figure 1:** Lymph node with increased volume, located in the left cervical region.



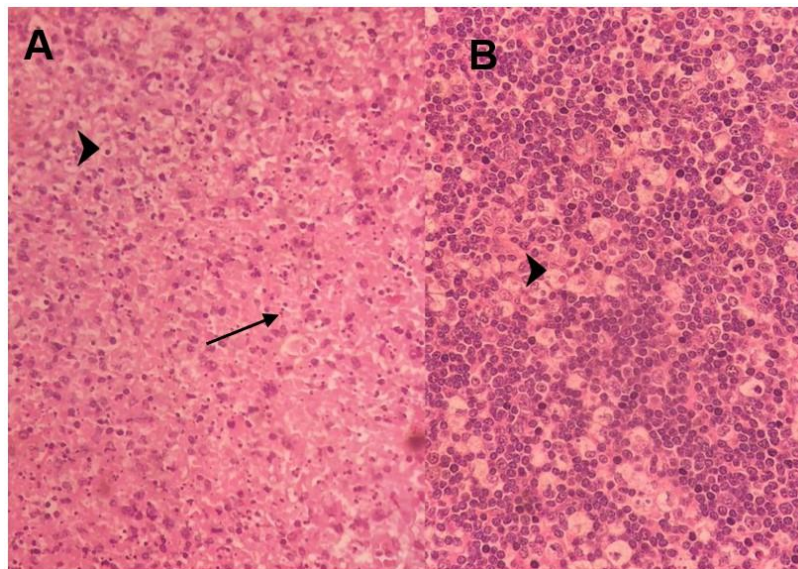
**Figure 2:** Contrast CT scan with contrast, showing evidence of multiple bilateral cervical lymphadenopathies, primarily on the left side.

The lymph node biopsy revealed chronic necrotizing lymphadenitis with a significant presence of histiocytes, with no evidence of granulomas, giant cells, or malignant neoplasm. (Fig. 3-4)

During the follow-up, serological studies for HIV, Epstein-Barr virus, toxoplasma, and cytomegalovirus were performed and were all negative. Finally, serology for antinuclear antibodies (ANA) was also negative.



**Figure 3:** (4x) Complete involvement of the lymph node, with alteration of its architecture, with pale irregular areas with granulomatous tendency, composed of histiocytes, plasmacytoid dendritic cells, eosinophilic granular material (arrowhead) and central non-caseating necrosis, which suggests Kikuchi-Fujimoto disease (arrows).



**Figure 4:** A. (10x), granular eosinophilic material and abundant karyorrhectic debris (nuclear dust) can be seen (arrowhead), often surrounding a central area of manifest necrosis (arrows). B. (4x) The regions between the pale areas include small lymphocytes mixed with immunoblasts and groups of plasmacytoid dendritic cells, giving a speckled or starry sky appearance. The histiocytes (arrowhead) include eosinophilic cytoplasmic phagocytic cells with crescent-shaped nuclei (crescent-shaped histiocytes) and non-phagocytic cells with twisted or reniform nuclei.

The patient received symptomatic treatment. The 30-day follow-up showed clinical improvement in the lymphadenopathies, which subsided entirely in the following weeks.

## Discussion

Kikuchi-Fujimoto disease is a rare disease characterized by necrotizing histiocytic lymphadenitis, which is generally self-limiting and has a benign course. It primarily affects young people under 30 years old, predominating women over men (Chung Ching, 2017). It can also manifest in the pediatric population, with a recurrence of up to 12.2% (Selvanathan *et al.*, 2020). Since nodal tuberculosis is a common condition in many countries, it is critical to identify KFD as a potential differential diagnosis and include it in diagnostic protocols as an important step.

Studies in the United States and Europe found distribution in all racial and ethnic groups. Human leukocyte antigen (HLA) genotyping studies showed a connection with HLA-DPB1 and HLA-DPA1 alleles in the Asian population (Ahmed *et al.*, 2021).

There are two theories about its etiology, including infectious and autoimmune causes. Many infectious, viral agents such as Epstein-Barr virus (EBV), *herpes simplex virus type 1 and 2* (HSV 1/2), *varicella-zoster virus* (VZV), *cytomegalovirus* (CMV), *human herpes virus* (HHV 6, 7, 8), *parvovirus B19*, *human papillomavirus* (HPV), *hepatitis B virus* (HBV), *human T-lymphotropic virus 1* (HTLV-1), *rubella*, *paramyxovirus* and *parainfluenza* may trigger the clinical picture; additionally, during the current pandemic, an association with *SARS-COV2* was found (Stimson *et al.*, 2021). There may also be bacterial triggers, including infections by *Brucella spp.*, *Bartonella henselae*, *Toxoplasma gondii*, *Yersinia enterocolitica*, *Entamoeba histolytica*, and *Mycobacteria species*. Regarding the autoimmune hypothesis, human leukocyte antigens (HLA) have been identified in populations that are more prone to developing this disease, including systemic lupus erythematosus (SLE), Sjogren's syndrome, Wegener's granulomatosis, rheumatoid arthritis, and Still's disease (Muhammad *et al.*, 2022).

Kikuchi disease has an acute or subacute onset, with symptoms developing throughout 2 to 3 weeks. Localized cervical lymphadenopathy is the most common clinical feature, with firm, tender, or painful lymph nodes, with firm, tender or painful lymph nodes. It mainly affects the cervical chain, although supraclavicular, axillary, thoracic, intraparotid, abdominal, and pelvic lymph nodes may also be involved (Mathew *et al.*, 2016). Lymphadenopathy is accompanied by mild fever, upper respiratory tract symptoms, and additional constitutional signs such as malaise, fatigue, anorexia, weight loss, night sweats, and chills (Dumas *et al.*, 2014).

For early and accurate diagnosis of the disease, it is essential to perform a proper medical history and to examine patients for any abnormalities. The two most relevant aspects are the clinical manifestations and pathological features. Tomographic imaging findings may be helpful but do not help in

the definitive diagnosis (Xu *et al.*, 2019) based on histopathological examination of the affected lymph node and ruling out other infectious and non-infectious pathologies. Three histologic stages of KFD have been proposed, the necrotizing, xanthomatous, and proliferative phases (Salamat *et al.*, 2020). An expanded paracortex characterized by sheets of histiocytes and dendritic cells with an initial proliferative pattern with plasmacytoids combined with karyorectic nuclear debris and small lymphocytes. The necrotic phase is characterized by the presence of necrosis, and the xanthomatous phase is dominated by foamy histiocytes in the lesions, irrespective of the presence or absence of necrosis (Perry and Choi, 2018). These pathognomonic morphological findings of the disease can be identified with immunohistochemistry for CD123 and TCL1 (nuclear reactivity) identified from the proliferation of plasmacytoid dendritic cells and karyorrhexis (Cuglievan and Miranda, 2017).

The treatment is aimed at symptomatic control, and non-steroidal anti-inflammatory drugs (NSAIDs) have been recommended for lymph node sensitivity or febrile illness (Cellura *et al.*, 2021). If it is severe, the use of glucocorticoids has been recommended, but there is no agreement among experts on the dosage or duration (Dumas *et al.*, 2014; Jang *et al.*, 2000).

## Conclusion

Kikuchi-Fujimoto disease remains a challenge for medical professionals. It should be included in the differential diagnoses of all patients presenting with adenopathies and febrile episodes of unknown origin, to avoid a greater number of medical consultations and the unnecessary administration of therapeutic drugs. The performance of a lymph node biopsy, with subsequent histological studies, is of great importance, and should be analyzed by an experienced pathologist.

**Author Contributions:** RVB, JQZ were involved in reviewing the literature and writing the article. RVB, LBP, MGQ and OGV were involved in the critical review of it. All authors verified the final version of the article.

**Financing:** None.

**Conflict of Interest:** None.

**Informed Consent:** The patient signed informed consent for the report of this case.

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