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Differential Diagnosis of Kikuchi-Fujimoto Disease: Rare Presentation of Histiocytic Necrotizing Lymphadenitis

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1. Abstract
Kikuchi-Fujimoto Disease (KFD), also known as Histiocytic necrotizing lymphadenitis, is a rare case of cervical lymphadenopathy. Patients usually present with localized lymphadenopathy, fever and fatigue.[2] Because of the poorly understood etiology, it can be mistaken for an infectious disease or even malignancy [2]. Here we discuss a case of KFD that initially presented with left sided cervical lymphadenopathy. Due to its characteristic overlap with other disorders like Tuberculuos lymphadenitis, bacterial lymphadenitis and lymphoma, KFD remains an arduous diagnosis for physicians. Therefore, one should be made aware of symptoms that can lead to misdiagnosis in patients.

2. Keywords: Lymphadenitis, Cervical lymphadenopathy, Tuberculosis, Lymphoma.

3. Introduction
Kikuchi-Fujimoto Disease (KFD) is known to occur both in the juvenile and adult with most cases reported in Asia, primarily affecting young female adults in their 20s and 30s. Kikuchi-Fujimoto disease is named after the Japanese pathologists who first described it in 1972[1]. Kikuchi-Fujimoto Disease is typically characterized by cervical lymphadenopathy. Less frequently, other symptoms might also be present like nausea, myalgia, arthralgia, night sweats and fatigue[1]. KFD is diagnosed via excisional lymph node biopsy and histopathological analysis(Sarfraz et al., 2021)[2]. Treatment is mostly symptomatic with antipyretics, non-steroidal anti-inflammatory drugs or on rare occasions, steroids; associated with spontaneous recovery in 1–6 months.

4. Case presentation
A 26y/o South East Asian female, Post COVID-19 (AstraZeneca) vaccinated status presented in our outpatient department in January 2022 with left-sided cervical lymphadenopathy with the presence of red erythematous maculopapular rashes at the neck region. This patient was reported with small bulging mass at the left side of her neck for one month. Associated symptoms included one month of low-grade fever, fatigue and arthralgia. There was no history of night sweats or significant weight loss. On presentation, the patient was hemodynamically stable with a temperature of 100.3 C, heart rate of 174 beats/min, respiratory rate was 24breaths/min and blood pressure was 120/74 mm/hg, SpO2 98% in RA .On physical examination there was diffuse right sided submandibular lymphadenopathy at cervical region C2, C3, C4. Lymph nodes were rubbery, soft and mobile. Her nose and throat examination were normal. On auscultation of the chest, breath sounds were normal bilaterally and normal heart sounds were present. The abdominal examination was also normal. Initial lab investigations included complete blood count with total and differential leukocyte count, biochemical profile, erythrocyte sedimentation rate (ESR) and lactate dehydrogenase (LDH). This was done to rule out any possibilities of lymphadenitis, or neoplastic disorder.

On laboratory examination there was an increase in lymphocytes percentage (40%) but no leukocytosis and an increase in inflammatory markers including lymphocytes, ESR and LDH. On histopathology examination lymphoid tissue with large area of necrosis with abundant karyorrhectic debris with plenty of lymphocytes and plasma cells with proliferative histocytes and inflammation were present, without presence of granuloma and typical features.

Table 1: Laboratory findings: Hematology

Variable	Reference range	Day 0	Day 30
Hemoglobin (g/dl)	12–16	10	11.2
Red blood cell count (million/c/mm)	3.5–5.5	4.49	4.06
Total leucocyte count (c/mm)	4000 - 11000	2000	10900
Hematocrit (%)	36–53	38.16	40.9
Mean corpuscular volume (fl)	80–100	85	83

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Mean corpuscular hemoglobin (pg.)	26–34	26.2	28
Mean corpuscular hemoglobin concentration (g/dl)	31–37	22.27	27.5
Platelet count (c/mm)	150000–450000	287000	291000
Erythrocyte sedimentation rate (mm/hr.)	0–20	65	19
lactate dehydrogenase (u/l)	120-400	536	384
Neutrophils (%)	54–62	73	76
Lymphocytes (%)	25–33	24	24
Eosinophil's (%)	01–06	3	0

Table 2: Laboratory findings: Biochemical Tests

Tests	Reference range	Result
Glucose – R/F	60-120 mg %	121
Urea	10-50mg/ dL	23
Creatinine	0.6-1.6 mg/dL	0.4
Amylase	100u/L	55
Sodium	135-145 mEq/L	137
Potassium	3-5mEq/L	4.5

Table 3: Biochemical test

Tests	Reference range	Result
Bilirubin Total	0.4- 1.0 mg %	0.9
Bilirubin Conjugated	0.1-0.4 mg%	0.3
Alanine Transaminase (GPT)	<45u/L	42
Alkaline Phosphatase	42- 128 U	76
Alanine transaminase (GOT)	<50u/L	26

A provisional diagnosis of Bacterial Lymphadenitis (Cat Scratch Disease) was made based on her history of being scratched by a street cat in her neck. Further investigations were ordered to determine the size and extent of the lymphadenopathy. These included ultrasonography of the neck and abdomen, to visualize any hidden lymphadenopathy that might have been missed during the initial physical examination; chest x-ray, to rule out any underlying conditions.

5. MRI Reporting: Normal MRI brain findings with diffuse disc bulge at C5-C6 and C6-C7 intervertebral levels without narrowing of lateral recesses.

6. On ultrasonography of neck:

THYROID: RIGHT LOBE: Normal in size measuring 16* 13.4* 32.5 mm. no calcification. No focal lesion. Vascularity appears normal. LEFT LOBE: Normal in size measuring 12.3* 15.8*30. No calcification. No focal lesion. Vascularity appears normal.

- Few tiny cystic lesion noted in both lobes of thyroid measuring 2.4*3.1 mm on left and 1.6* 2.5mm on right.
- Few lymph nodes noted at level II/III/IV cervical region, largest measuring 6.3*9.8mm (right side)
- Colloidal cyst in bilaterally lobes.

The rest of the ultrasound report did not show any abnormalities. Chest x-ray was normal and interferon-gamma release assay (IGRA) was not conclusive due to patient's weak financial status.

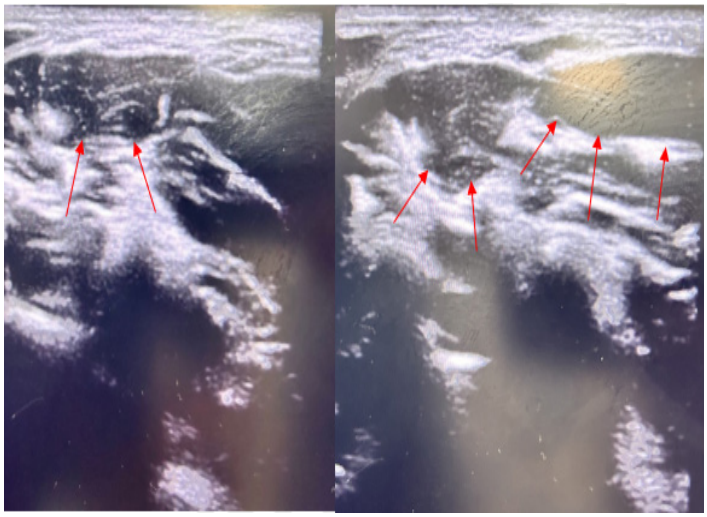

Fig: 1: Ultrasound of neck showing enlarged cervical lymph nodes (Left side). Lymph nodes in usg are hypo echoic in normal.

To get more clarity, an excisional lymph node biopsy from the anterior cervical chain was performed and on histopathological analysis it showed necrotizing lymphadenitis with partial alteration of structure by clusters of histiocytic and interspersed nuclear debris. In preserved areas, lymphoid follicles with pale staining germinal centers were noted. On Warthin starry silver stain, Bartonella henslae were not seen neither any evidence of Tuberculuos granulomas or malignancy was found. The culture did not reveal any growth. No infection work up were performed.

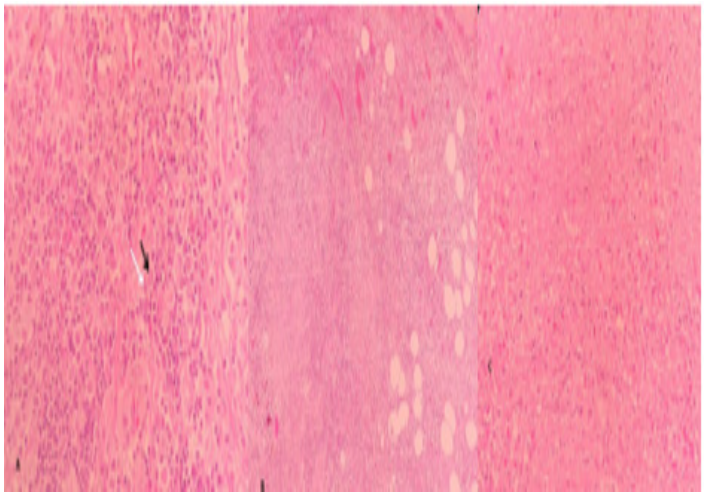

Fig: 2: H&E stain section of a lymph node showing interfollicular/ paratrabecular areas rich in histiocytes (white arrow) admixed with apoptotic bodies (black arrow)- (A) high magnification, (B)

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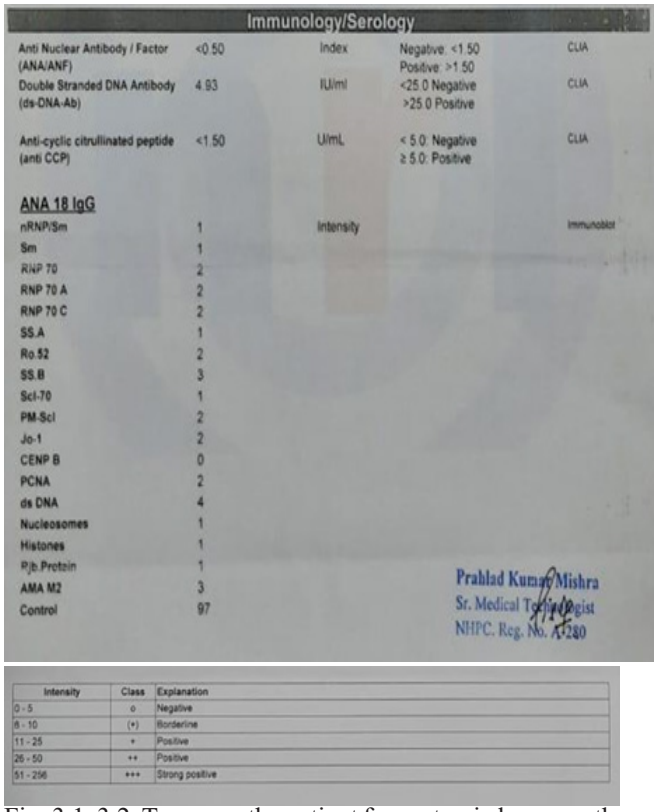
low magnification

(C) H&E stain sections showing mildly enlarged lymph node.



Immunology/Serology

Anti Nuclear Antibody / Factor (ANA/ANF)	<0.50	Index	Negative: <1.50 Positive: >1.50	CLIA
Double Stranded DNA Antibody (ds-DNA-Ab)	4.93	IU/ml	<25.0 Negative >25.0 Positive	CLIA
Anti-cyclic citrullinated peptide (anti CCP)	<1.50	U/mL	< 5.0: Negative ≥ 5.0: Positive	CLIA
ANA 18 IgG				
nRNP/Sm	1	Intensity		Immunoblot
Sm	1			
RNP 70	2			
RNP 70 A	2			
RNP 70 C	2			
SS.A	1			
Ro 52	2			
SS.B	3			
Scl-70	1			
PM-Scl	2			
Jo-1	2			
CENP B	0			
PCNA	2			
ds DNA	4			
Nucleosomes	1			
Histones	1			
Rib Protein	1			
AMA M2	3			
Control	97			

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Intensity	Class	Explanation
0 - 5	o	Negative
6 - 10	(+)	Borderline
11 - 25	+	Positive
26 - 50	++	Positive
51 - 256	+++	Strong positive

Fig: 3.1, 3.2, To screen the patient for systemic lupus erythematous (SLE), antinuclear antibody and anti-dsDNA tests were performed, all of which were negative.

7. Treatment

It was decided for fever, 500mg Dovopar thrice a day , for allergic symptoms Tab. Sufex 180 mg oral once a day, for anti-bacterial effect Inj monocef 2gm twice daily, for subsiding pain Inj ketorolac 30mg thrice daily, for GERD Tab Rabeloc 20 mg twice daily was administered for one and half months. He was started on prednisolone 40 mg once daily after breakfast due to persisting lymph node that was not subsided by NSAIDS, his lymph node size started regressing after 6 days and steroid was continued for 3 weeks followed by tapering dose and stop. He is under regular follow up and observation every 6 monthly in our outpatient clinic to monitor any spread of the lymphadenopathy. The disease course was uneventful. The patient was not given any further medication and watchful waiting was continued. Within 45 days, the lymphadenopathy decreased dramatically, and the patient reported no fever. It completely disappeared in three months.

8. Discussion

The actual etiology of KFD is still unknown but it has been proposed to have infectious and immunological etiologies. Some of the unidentified agents may include toxoplasmosis, Brucella, Bartonella henslae, Yersinia enterolitica, human herpes virus, Epstein-Barr virus, Human T lymphocytes Virus, paramyxovirus, parvovirus B19, cytomegalovirus and human immunodeficiency virus. Kikuchi and Fujimoto reported the first case of KFD in 1972 and described it as lymphadenitis with reticular cell proliferation and abundant phagocytes and histocytes, suggesting benign histiocytic necrotizing lymphadenitis.

Prevalence of Kikuchi disease has been seen highest amongst the Japanese population and people from East Asia but more recently this disease has been reported all over the world . Our case is from South Asia, Nepal.

As reported by Roberto N. Miranda in “Atlas of Lymph Node Pathology”, clinical course of this disease has some specific and non-specific features with the specific one being unilateral cervical lymphadenopathy in our patient and nonspecific being fever, anorexia, leukopenia and arthralgia. Several differential diagnoses are associated with this presentation.

Confirmation of diagnosis is done by lymph node biopsy and histopathological analysis which showed necrotizing lymphadenitis with partial alteration of structure by clusters of histiocytic and interspersed nuclear debris. In addition, there is presence of proliferating histiocytic, T lymphocytes (CD8) and immunoblasts.

The minimum criteria for KFD diagnosis is presence of aggregated histiocytic with occasional crescent-shaped nuclei, plasmacytoid histiocytic and scattered karyorrhexis. The biopsy results of our patient were quite similar, making KFD our primary diagnosis. Due to similar clinical characteristics, KFD is often mistaken for lymphoma, tuberculosis, systemic lupus erythematous, bacterial lymphadenitis and even metastatic adenocarcinoma. Therefore, any physician who comes across a case of lymphadenopathy, should keep KFD in mind when consider differential diagnoses. KFD is self-limiting and resolution occurs is one to six months. There are no specific drugs for KFD and usual treatment is symptomatic, consisting of antipyretics, analgesics and corticosteroids are reserved for severe cases or where supportive measures fail to control symptoms. Overall, the disease course is benign with spontaneous self-resolution within weeks to months and a 3-4% low recurrence rate.

9. Conclusion

This case report elucidates the clinical presentation, diagnostic challenges, and management of Kikuchi-Fujimoto Disease (KFD) in 26-year-old South East Asian female following her COVID-19 vaccination. The patient presented with left-sided cervical lymphadenopathy, accompanied by erythematous maculopapular rashes on the neck, low-grade fever, fatigue, and arthralgia. These symptoms plus laboratory findings indicated an increased lymphocyte counts and elevated inflammatory markers, initially suggested an infectious or inflammatory etiology.

The differential diagnosis included various conditions such as bacterial lymphadenitis, tuberculosis, and malignancies. However, the absence of significant weight loss, night sweats, and the normal findings on chest x-ray and ultrasonography, which ruled out major neoplastic or infectious disorders, were crucial in narrowing down the diagnosis. The histopathological examination of the excisional

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lymph node biopsy was instrumental in confirming KFD. The biopsy revealed necrotizing lymphadenitis with extensive necrosis, abundant histiocytes, and karyorrhectic debris, without granulomas or malignancy. These findings were consistent with KFD, distinguishing it from other potential diagnoses such as tuberculosis, lymphoma, or systemic lupus erythematosus.

Given the provisional diagnosis of KFD, the patient was managed with symptomatic treatment. Initial management included antipyretics and analgesics for fever and pain. Due to persistent lymphadenopathy despite NSAIDs, corticosteroids were introduced. Prednisolone was administered for a three-week period, resulting in significant regression of lymphadenopathy and symptomatic relief. The patient's condition improved substantially within 45 days, and complete resolution of symptoms occurred within three months. This is consistent with the known self-limiting nature of KFD, where spontaneous resolution typically occurs within one to six months.

The case underscores several important clinical considerations. Firstly, Kikuchi-Fujimoto Disease should be considered in the differential diagnosis for patients presenting with unilateral cervical lymphadenopathy, particularly when accompanied by systemic symptoms such as fever and fatigue, and in the context of recent vaccinations or infections. Secondly, accurate diagnosis of KFD relies heavily on histopathological analysis of lymph node biopsy, which is crucial in distinguishing KFD from other similar conditions. The characteristic findings of necrotizing lymphadenitis with abundant histiocytes and karyorrhexis are pivotal for confirming the diagnosis and guiding appropriate management.

Moreover, this case highlights the importance of symptomatic treatment in managing KFD, as there are no specific antiviral or antimicrobial therapies for this condition. Corticosteroids can be beneficial in cases with significant symptoms or persistent lymphadenopathy, while regular follow-up is essential to monitor for disease resolution and potential recurrence. The benign course and low recurrence rate of KFD support a conservative management approach, with resolution typically occurring within a few months.

In conclusion, this case illustrates the necessity of considering KFD in the differential diagnosis of cervical lymphadenopathy with systemic symptoms. Comprehensive diagnostic evaluation, including histopathological examination, is crucial for accurate diagnosis and management. Understanding the clinical course and management strategies for KFD can aid clinicians in providing effective care and avoiding unnecessary interventions.

Credit Authorships contribution statement:

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