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Positive Autoimmune Markers in Kikuchi-Fujimoto Disease in a 12-Year-Old Female: A Case Report

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ABSTRACT: Kikuchi-Fujimoto Disease (KFD), also known as histiocytic necrotizing lymphadenitis, is a rare, benign, and typically self-limiting entity characterized by regional lymphadenopathy and fever. While it is more commonly seen in young adults, specifically of Asian descent, its occurrence in the pediatric population and the potential observation of autoimmune phenomena, remain compelling clinical curiosities. We report a case of a 12-year-old Saudi female who had presented to our hospital with a one-month history of intermittent fever, significant weight loss (10 kg), and a four-month history of painful cervical lymphadenopathy. Labs showed markedly elevated lactate dehydrogenase (LDH) and ferritin, severe vitamin D deficiency, and a positive autoimmune profile of antibody, including Antinuclear Antibody (ANA), Anti-RNP/Sm, and Anti-Sm. The patient underwent a significant histopathological and microbiological workup, including a negative PCR for Mycobacterium tuberculosis, arrived at a diagnosis of KFD. This case illustrates both the diagnostic challenges KFD poses in the pediatric population, where it can resemble malignancy or/or tuberculosis, and the significance of monitoring for systemic lupus erythematosus (SLE) in individuals with autoimmune markers present.

1. INTRODUCTION AND RATIONALE

Kikuchi-Fujimoto Disease (KFD) is a clinicopathological entity initially described independent of each other by Kikuchi and Fujimoto in 1972. It is primarily viewed as a benign entity of unknown origin or mechanism that is, as its name implies, primarily identified as necrotizing lymphadenitis, and more frequently cervical lymph nodes. Although KFD is prevalent worldwide, it is more commonly presented in East Asian populations, with a female to male ratio often cited as 4:1. In Saudi Arabia, KFD is thought to be rare, with one report indicating only approximately 0.5% of all lymph node biopsies are attributed to KFD.

The clinical significance of KFD stems from the appearance it can provide of more serious conditions, including malignant lymphoma and infectious etiologies (i.e., tuberculosis) and SLE (1). The resemblance to a more serious condition can lead to lengthy workups and delays in treatment. In pediatric patients, it can present, at times, aggressively, with high-grade fevers and profound constitutional symptoms in children that require a broad differential diagnosis (2).There are two rationales for presenting this case. The first is that KFD in the pediatric population of the Middle East is relatively uncommon and the patient reported a substantial constitutional symptom of weight loss (10 kg) which is atypical for a benign condition; therefore, it was

an area of interest to discuss with colleagues. The second rationale is that the patient had the presence of highly specific autoimmune markers, including Anti-Sm, which provokes the question of whether KFD is related to SLE, as some authors have posited that KFD may represent a manifestation of SLE or potential development (3). Therefore, this case provides an opportunity to discuss whether the presence of positive serology for autoimmune markers warrants long-term rheumatological follow-up in pediatric patients diagnosed with KFD.

2. EMERGENCY ROOM PRESENTATION

2.1 History and Clinical Picture on Admission

A 12-year-old Saudi girl, previously well with no notable past medical or surgical history, was presented to the Emergency Department (ED) for the second time in 2 weeks. She had been complaining of an ongoing fever for 1 month and increasing neck swelling. The girl had been experiencing daily alternating fevers for the last month, along with generalized weakness, body aches, and significant decreased eating and oral intake. She has also had an unintentional weight loss of about 10 kg in the last 3 months.

Furthermore, the girl was experiencing a headache in the back of her head for 1 month, which occurred mostly early in the morning. This headache was associated with photophobia, dizziness when standing, nausea, and non-projectile vomiting. Four months prior to her admission, she had experienced a painful swelling on the left side of her neck, which had been progressively enlarging. There were no further symptoms reported related to constitutional signs, such as night sweats or cough nor any known contact with persons with tuberculosis.

Upon physical examination, the girl appeared unwell and pale and was severely underweight despite being hemodynamically stable. However, she appeared cachectic. The neck examination showed a left posterior cervical chain node that was 3 × 2 cm, tender, firm and progressively enlarging. There were no signs of generalized lymphadenopathy, hepatosplenomegaly or swollen joints. Cardiovascular and respiratory examination were unremarkable. The neurological examination showed cranial nerves intact and no focal neurological findings or signs of meningeal irritation.

2.2 Laboratory Workup and Findings

Her initial laboratory workup also demonstrated a few significant abnormalities. The hematological studies showed a normal white blood cell count but there were biochemical markers of high inflammatory necrotic process. LDH was high at 712.27 U/L (reference range: 140-270U/L) and ferritin was high at 641.50 μg/L (reference range: 11-306.8 μg/L). Both of these markers are typically raised in KFD due to macrophage activation and cellular turnover and are stated to occur in KFD.

The patient had also demonstrated a severe vitamin D deficiency with a 25-hydroxy vitamin D of 10.54 nmol/L (reference range: 75-250 nmol/L). C-reactive protein (CRP) was relatively low at 1.85 mg/L which is sometimes seen in KFD even at high fever. To rule out possible infectious diagnoses, a biopsy was taken for culture. The PCR for Mycobacterium tuberculosis DNA complex was negative and no acid fast bacilli were seen on stain.

An immunology profile was also obtained that showed some striking and possibly contradictory lab results. The antinuclear antibody (ANA) screen was positive. Further sub-serology studies of the profile showed the patient was positive for Anti-RNP/Sm, Anti-Sm and Anti-RNP. Anti-dsDNA, Anti-SSA and Anti-SSB were negative. The significance of Anti-Sm is important since it's highly specific for SLE (4).

2.3 Complement System and Renal Function

The complement system is a vital component of the innate immune response, consisting of a cascade of proteins that enhance the ability of antibodies and phagocytic cells to clear pathogens and damaged cells. C3 and C4 are among the most frequently measured complement proteins; C3 is the most abundant and central to all activation pathways, while C4 is primarily involved in the classical and lectin pathways. In clinical practice, monitoring these levels is essential for assessing inflammatory and autoimmune activity. Low levels of C3 and C4 often indicate consumption due to active immune complex formation, a hallmark of diseases such as systemic lupus erythematosus (SLE).

The low C4 level in this patient, while C3 remains within the normal range, is a significant finding that may suggest early classical pathway activation, consistent with the positive autoimmune markers observed. The negative 24-hour urine protein result is reassuring, indicating no current evidence of significant lupus nephritis or renal impairment at this stage.

Table 1: Summary of Laboratory Investigations

Test Name	Result	Reference Range	Status
Glucose Random	5.4 mmol/L	3.9 - 11.0	Normal
Amylase	116.30 U/L	28.0 - 100.0	High
LDH	712.27 U/L	140.0 - 270.0	High
Alkaline Phosphatase	65.70 U/L	46.0 - 116.0	Normal
Albumin	39.9 g/L	34.9 - 47.5	Normal
ALT (GPT)	46.0 U/L	< 40.0	High
Ferritin	641.50 ug/L	11.0 - 306.8	High
25 OH Vit.D	10.54 nmol/l	75.0 - 250.0	Low
C-Reactive Protein (HS)	1.85 mg/L	0.0 - 5.0	Normal
ANA Screen	Positive	Negative	Abnormal
Anti-dsDNA Ab	Negative	Negative	Normal
Anti-Sm	Positive	Negative	Abnormal
Anti-RNP/Sm	Positive	Negative	Abnormal
C3 Complement	1.35 g/L	0.8 - 1.7	Normal
C4 Complement	0.06 g/L	0.15 - 0.57	Low
24-Hour Urine Protein	Negative	Negative	Normal

3. MANAGEMENT STRATEGIES

3.1 Initial Management Plan and Symptomatic Control

The initial management plan was to provide symptomatic control, and rule out life-threatening conditions. Given the significant weight loss, and localized lymphadenopathy, the primary concerns were malignancy (such as lymphoma) or a chronic infection (such as tuberculosis) (1). The patient was started on paracetamol for fever and headache, which resulted in partial symptom relief. KFD is generally a self-lapsed condition, and in mild cases it is common to use non-steroidal anti-inflammatories (NSAIDs) to control fever and tenderness of lymph nodes (5). However, in the case of this patient, the degree of her constitutional symptoms- that is, her 10 kg weight loss, and degree of inflammatory markers (LDH and Ferritin), suggested a more aggressive clinical course. Thus, the medical team contemplated early corticosteroid use to prevent a hyper-inflamatory response.

3.2 Hospital Course and Follow-Up Outcomes

During the hospital course, a diagnosis of KFD was substantiated as she did not have tuberculosis, and the clinical concerns aligned with necrotizing lymphadenitis. The patient's management was escalated to glucocorticoids, which are certainly reserved for severe cases or symptomatic persistent cases. The institution of glucocorticoids among KFD patients have been documented

to correlate with expeditious fever resolution and improved lymphadenopathy (2).Due to the patient's positive autoimmune markers (ANA, and Anti-Sm), she was earranged for pediatric rheumatology service evaluation. The patient did not satisfy the full American College of Rheumatology (ACR) criteria for definitive diagnosis of SLE at initial presentation, but given she had Anti-Sm antibodies that would require a treatment paradigm. Hydroxychloroquine was suggested in conjunction with current issues of immune dysregulaition, but also as a preventive paradigm of preventing SLE.The patient experienced gradual clinical improvement, resolution of fever, and the cervical lymphadenopathy tenderness reduced. Follow-up was arranged for her weight gain, pubertal development, and any potential new autoimmune symptoms. The prognosis is generally good as KFD has relapse rates of 3% - 4%, but the association with SLE will require longer term serological and clinical assess.(6)

4. DISCUSSION

4.1 Epidemiology and Clinical Features of Kikuchi-Fujimoto Disease

Kikuchi-Fujimoto Disease remains a cryptic condition, predominantly affecting young females, generally younger than 30 (5). It is primarily prevalent in Asia, but more recent reports from other areas have emerged from the Middle East and Africa (7). A case series, including 920 lymph node biopsies from Saudi Arabia, did note only 0.5% of patient cases had KFD, but illustrates how rare KFD is in Saudi Arabia.The clinical presentation of KFD is primarily characterized by cervical adenopathy, which is detected in 60% to 90% of people (8). Nodes are commonly tender and range in size from 1 cm to 4 cm. Fever is the predominant systemic feature of KFD and occurs in approximately 30% to 50% of cases. However, this particular case of a 12-year-old child stands out with the extreme severity of vital symptoms. A 10 kg weight loss, noted in a child, is highly significant and often suggests malignancy or a chronic infectious process (such as tuberculosis) (1). Laboratory evaluation of KFD is frequently non-specific but may demonstrate features of the underlying necrotizing process. However, the elevated LDH and ferritin levels demonstrated in this patient reflect the substantial karyorrhexis and the cystosolic proliferation of histiocytes within the lymph nodes. Leukopenia is also a common association of KFD and exists in up to 50% of patients, even though it was not the predominant finding in this case (2). The presence of severe vitamin D deficiency (10.54 nmol/L) is noteworthy; vitamin D may play an important role in modulating immune responses, and its deficiency can lead to loss of self-tolerance or exaggeration of inflammatory responses.

4.2 Interpretation of Positive Autoimmune Serology in Pediatric KFD

One of the most important aspects of this case is the positive autoimmune markers; most notably, ANA, Anti-RNP/Sm, and Anti-Sm. The relationship between KFD and SLE is complicated and debated in the literature. KFD can predate, be concomitant with, or can follow the diagnosis of SLE (9). Some authors have suggested that KFD is an example of a microscopic or localized form of SLE (10).

The presence of Anti-Sm antibodies is highly relevant. Anti-Sm is a highly specific test for SLE and the presence of the marker in a patient with KFD would suggest an underlying autoimmune process (4). In pediatric cohorts, ANA positivity has been noted in up to 71% of KFD patients, with some having concurrent SLE at presentation (2). The "antigen release theory" postulates that the significant cellular necrosis occurring at the lymph node in KFD could release intracellular antigens (i.e. Sm and RNP) that genetically pre-disposed patients may develop autoantibodies (4).

While it is possible for patients with KFD and autoantibodies to have a transient serological conversion that may resolve with lymphadenitis, there is a chance that other patients will go onto develop a systemic autoimmune disease (4). Therefore, the presence of Anti-Sm in this 12-year-old patient cannot be dismissed as a transient phenomenon. This requires a heightened clinical concern and potentially lifelong follow-up for clinical features of SLE such as malar rash, photosensitivity, arthritis, or renal involvement (9). Currently, hydroxychloroquine in these scenarios is being considered a validity option and valid strategy to approach the KFD-SLE interface.

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6. CONCLUSION

Though rare, Kikuchi-Fujimoto Disease is an important consideration in the differential diagnosis of cervical lymphadenopathy and fever of unknown origin in pediatrics. This case illustrates that KFD can present with severe constitutional symptoms, including significant weight loss, which could be mistaken for more serious conditions, such as lymphoma or tuberculosis. Positive autoimmune markers, especially Anti-Sm, in a pediatric patient with KFD represents an important clinical finding that supports a strong association with systemic lupus erythematosus.

The management of KFD in children will depend on the severity of symptoms. While the disease is often self-limiting, corticosteroids and possibly hydroxychloroquine should be considered in cases with marked systemic involvement, or a positive autoimmune profile. Pati\e\nts will require long-term follow up to look for possible development of SLE. Early recognition and a multi-disciplinary approach between pediatricians, pathologists, and rheumatologists is paramount for optimal outcomes and avoidance of unnecessary, invasive procedures.This longitudinal surveillance is particularly vital given that the immune dysregulation observed in Kikuchi-Fujimoto disease may overlap with or precede the clinical manifestations of systemic lupus erythematosus. Systematic monitoring should prioritize the reassessment of serological markers and clinical signs of connective tissue disorders to ensure that any progression toward a chronic autoimmune pathology is identified at an early stage. Such a proactive diagnostic framework allows for the timely adjustment of therapeutic interventions, thereby mitigating potential long-term morbidity in pediatric populations.

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