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Case Report

Misled by the Xpert-Kikuchi's disease masquerading as tuberculosis

Aparna Krishnakumar*, Elayaraja Sivaprakasam, Latha Ravichandran, Umapathy Pasupathy, Sarala Premkumar, Ram Mohan

Department of Paediatrics, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India

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***Correspondence:**
Dr. Aparna Krishnakumar,
E-mail: aparnakrishnakumar5@gmail.com

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ABSTRACT

Kikuchi-Fujimoto disease (KFD), also called histiocytic-necrotizing lymphadenitis is a rare, idiopathic and self-limiting cause of lymphadenitis. Clinical presentation of KFD closely resembles nodal tuberculosis (TB). Here we present a case of an adolescent female whose diagnosis of KFD was made despite being misled in the course. A 15-year-old female, previously treated for tuberculous lymphadenitis was brought with complaints of fever for 1 month. Various possibilities considered were TB reactivation, autoimmune disorders, lymphoma. Lymph node biopsy for gene Xpert showed TB bacilli detected but low with no RIF resistance. Despite anti tuberculous treatment initiation, there was no improvement in the clinical condition. Histopathology of cervical node showed features of Kikuchi lymphadenitis. Literature search revealed that gene Xpert can detect the intact DNA of *Mycobacterium tuberculosis* even years after the previous treatment. On stopping anti tuberculosis therapy (ATT) and starting IV steroid, she started improving dramatically. KFD should always be kept as a differential diagnosis in any individual with fever and lymphadenopathy. Diagnosis can be misled in any patient based on gene Xpert reports alone which often turns out to be positive if there is past history of TB as gene Xpert detects DNA from non-intact cells suggesting that dead bacilli contribute to the false positivity.

Keywords: Gene Xpert, False positivity, Dead bacilli, Kikuchi

INTRODUCTION

Kikuchi-Fujimoto disease, or histiocytic necrotizing lymphadenitis, is a rare and benign disorder that mainly affects women under 40 years. This clinicopathological entity, first described in 1972, is characterized by fever and painful regional, predominantly cervical lymphadenopathy. Histologically, involved lymph nodes exhibit paracortical areas of apoptotic necrosis with abundant nuclear debris and a proliferation of histiocytes, plasmacytoid dendritic cell, CD8+T, but no neutrophils.[1] Although its etiology is unknown, autoimmune mechanisms or abnormal responses to viruses were proposed.[2]

In the Indian subcontinent, this presentation closely mimics TB. However histopathological examination of the lymph node forms the mainstay in establishing the diagnosis whereas gene Xpert helps in the diagnosis of TB. Here we present an interesting case of KFD, that shared many similarities with TB in its clinical presentation and lab investigation.

CASE REPORT

A 15-year-old female presented to the outpatient department with complaints of fever and vomiting for 1 month. She had a history of swelling in the neck in 2016 which was diagnosed as TB lymphadenitis after fine needle aspiration cytology (FNAC) and biopsy for which she completed six months course of ATT. In May 2019, she was evaluated at a local hospital for complaints of fever with rash for 20 days associated with cervical lymphadenopathy. Despite being treated outside with

antibiotics, she persisted to have fever spikes, due to which she got admitted at our center for further evaluation.

On examination, she fell into the category of severe thinness as per WHO (BMI-12.6), though there was no history of documented weight loss. She had multiple lymph nodes in the neck and axilla, largest being 3x2 cm which were non tender nor matted with erythematous macules over face, arms, trunk. The possibilities considered were TB reactivation due to previous history of TB, autoimmune disorders as this was an adolescent female with pyrexia of uncertain origin (PUO) and skin rashes, lymphoreticular malignancy in view of fever, weight loss and lymphadenopathy, retroviral infection as she was severely thin with PUO, KFD (Table 1).

Table 1: Investigations done for PUO work up.

Investigation	Results
Infectious disease	Negative
Retroviral	Negative
Antinuclear antibodies (ANA)	Negative
Repeat ANA	Negative
Complement C3, Complement C4 (C3, C4)	Normal
Bone marrow biopsy	Hypo cellular Reactive marrow
Bone marrow aspiration	Hypo cellular Reactive Marrow
Bone marrow aspiration for fungal elements	Negative
Sputum for gene Xpert	Negative
Sputum smear for AFB	Negative
Lymph node culture	No growth

Initial lab investigations done showed bicytopenia (Hb-9.5g/dl, total count (TC)-1800 cells/mm^3), elevated erythrocyte sedimentation rate (ESR) (72 mm), and elevated lactate dehydrogenase (LDH) (1172 units/L), chest roneograph was normal, Mantoux was negative.

Lymph node biopsy sent for gene Xpert detected MTB (very low). Based on this report, a diagnosis of extrapulmonary TB was made and she was started on ATT. Due to persisting fever after 72 hours of starting ATT, immune reconstitution inflammatory syndrome (IRIS) was suspected she was started on, Naproxen. Despite these measures she continued to have persistent fever spikes with fall in hemoglobin, leucocytes and platelets, she was started on IV methylprednisolone in view of suspected macrophage activation syndrome (MAS).

Meanwhile the histopathology report (Figure 1 and 2) of the biopsy sample confirmed the diagnosis of KFD. The histopathology findings were areas of focal necrosis containing macrophages with ingested debris. With the diagnosis made, she was treated with IV steroids which was later changed to oral steroids which was eventually tapered and stopped.

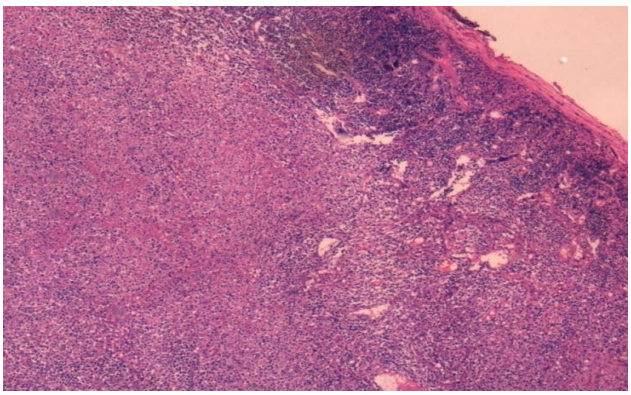

Figure 1: Lymph node biopsy with hematoxylin and eosin stain of areas of necrosis.

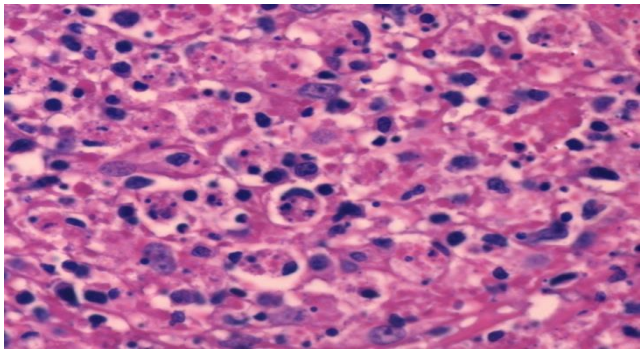

Figure 2: Lymph node biopsy of macrophages with ingested debris.

Three questions remained unanswered on obtaining the diagnosis: What was the reason for clinical worsening? Will starting steroids/ATT worsen bicytopenia in KFD? And can KFD present along with MAS? Extensive search through multiple articles helped in providing answers to the above questions.

DISCUSSION

Due to the similarities in the presentation of KFD and TB, KFD should always be borne in mind if any adolescent female presents with PUO and lymphadenopathy. Many cases have reported anemia with elevated LDH and ESR which was consistent with the lab findings in our patient.[2,3] Such a presentation of KFD with a significant past history like our patient sheds light into the following discussion supported by other studies.

As the course of management in this patient was misled by the presence of MTB bacilli in gene Xpert, despite being low, the following statement from a study done by Theron et al emphasizes on a very important point-the persistence of PCR positivity in the absence of culturable bacilli may cause Xpert positive after treatment

completion. This is based on the fact that gene Xpert detects DNA from non-intact cells suggesting that dead bacilli contribute to the false positivity. Xpert positivity in previously treated patients were transient and about half transitioned to Xpert negative after retesting within two months as per the study done by Theron et al.[4] However, in this patient, gene Xpert detected the presence of dead bacilli two year after completion of the treatment. There were no studies to support this late detection of bacilli in gene Xpert. These findings provide evidence of the low specificity of gene Xpert.

Even though KFD is a self-limiting condition, usually resolving within 4 months, a low recurrence rate of 3 to 4% has been reported.[5] As patient had a previous similar history, with no previous documents stating size of Mantoux or sputum showing acid fast bacilli (AFB), a possibility of misdiagnosed Kikuchi, in 2016 can be considered. Similarities between these two conditions in a country endemic for TB may bias the treating physician towards starting ATT.

The suspicion of MAS coexisting with KFD as in our patient was supported by a study done by Ahn et al which stated that KFD patients with MAS experienced longer hospital stays and worse hospitalization outcomes, including higher rates of intensive care unit stays and in-hospital mortality than in patients without MAS. In addition, the proportion of patients with KFD requiring glucocorticoid treatment was significantly higher in patients with MAS than in patients without MAS.[6]

Despite previously stating that histopathological examination is the main stay in the diagnosis of KFD, there are other histological differential diagnosis such as lymphoid malignancies particularly non-Hodgkin's lymphomas, lymphadenopathy due to autoimmune disorders, primarily systemic lupus erythematosus (SLE) and infectious etiologies, such as Epstein-Barr virus, herpes simplex virus, Bartonella henselae and toxoplasmosis.[7] Hence experience and consultation with a senior pathologist is a must before providing a report of KFD.

CONCLUSION

KFD should always be kept as a differential diagnosis in any individual with fever and lymphadenopathy. In a country like India where Tuberculosis is widely prevalent, it is not uncommon to find patients who have been previously on ATT. In such patients who have a similar presentation diagnosis can be misled based on gene Xpert reports alone which often turns out to be positive as gene Xpert detects DNA from non-intact cells suggesting that dead bacilli contribute to the false positivity. Interpretation of Xpert positivity in patients with previous TB should be considered after ruling out conditions with similar presentation such as KFD.

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