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CASE REPORT

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Kikuchi-Fujimoto disease following SARS-CoV-2 infection: A rare disease with increased incidence during the COVID-19 pandemic?

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Abstract

Kikuchi-Fujimoto Disease (KFD), also known as Kikuchi disease or Kikuchi histiocytic necrotizing lymphadenitis, is a rare and self-limiting condition characterized by cervical lymphadenopathy and fever, primarily affecting young Asian adults. The aetiology of KFD remains unknown, although various infectious agents have been suggested as potential triggers. With the emergence of the COVID-19 pandemic, cases of post-COVID-19 KFD and post-COVID-19 vaccine KFD have been reported. In this article, we present the first case of post-COVID-19 KFD in Hong Kong. A 24-year-old man developed fever and painful neck swelling 1 month after recovering from COVID-19. Diagnostic evaluation, including ultrasound-guided fine needle aspiration cytology (FNAC), confirmed the diagnosis of KFD. The patient's symptoms resolved spontaneously with supportive care. This case underscores the importance of considering KFD as a potential differential diagnosis in patients presenting with cervical lymphadenopathy and fever following COVID-19 recovery or vaccination.

KEYWORDS
COVID-19, Kikuchi disease, Kikuchi-Fujimoto disease, lymphadenopathy, *maximum*, SARS-CoV-2

INTRODUCTION

Kikuchi-Fujimoto disease (KFD), also known as Kikuchi disease or Kikuchi histiocytic necrotizing lymphadenitis, was first described in 1972 by Kikuchi and Fujimoto et al. almost simultaneously.[1] It is a rare, self-limiting and benign condition of unknown aetiology. The disease is characterized by cervical lymphadenopathy and fever, and primarily affects young Asian adults.[2,3] Numerous viruses, bacteria, mycobacteria, and parasites have been suggested as potential causative agents of KFD, but the connection between microorganisms and KFD remains inconclusive.[4] COVID-19, the disease caused by SARS-CoV-2 infection, was suggested to trigger KFD.[5] Cases of post-COVID-19[5–17] KFD and post-COVID-19 vaccine[18–30] KFD have emerged in recent years. In this article, we report the first case of post-COVID-19 KFD in Hong Kong.

CASE REPORT

A 24 year old obese man with past medical histories of allergic rhinitis, eczema and appendicitis presented to our unit for fever and painful neck swelling in January 2023, 1 month after he was diagnosed with COVID-19 by rapid antigen test. His COVID-19 symptoms were mild in December 2022 and resolved without anti-viral drugs, but the fever persisted, which prompted him to seek medical help. Apart from fever, he also complained of a one-day history of painful neck swelling. He was otherwise well with no complaint of respiratory, urinary, gastrointestinal, rheumatological or neurological symptoms. Physical examination revealed enlarged bilateral tender cervical lymphadenopathy without hepatosplenomegaly nor enlarged tonsils. His cardiovascular, respiratory, and neurological examinations were unremarkable.

Blood tests showed a raised lactate dehydrogenase level of 325 U/L (reference range ≤ 250 U/L) and a raised c-reactive protein level of 19 mg/L (refence range <5.0 mg/L). Other blood tests were unremarkable, including complete blood count with peripheral smear, renal function, liver function, procalcitonin, monospot test, immunoglobulin pattern, immunoglobulin G4 level and serum protein electrophoresis. Autoimmune markers including anti-nuclear antibody, anti-extractable nuclear antigen antibody, anti-neutrophil cytoplasmic antibody, rheumatoid factor and anti-cyclic citrullinated peptide antibody levels were within normal ranges. The chest x-ray was clear, and the electrocardiogram showed sinus tachycardia of 130 beats per minute with no other abnormalities.

Empirical treatment with Piperacillin/tazobactam was initiated with no improvement in fever nor bilateral cervical lymphadenopathy. The most prominent one was a right high cervical lymph node, measuring 1.72 cm × 0.84 cm in diameter by ultrasound. Fine needle aspiration of the right high cervical lymph node was performed on the third day after admission (31st day after COVID-19 diagnosis), with a total of 3 passes made with a 22G BBraun Spinocan® Quincke needle. The histopathology exam of the lymph node aspirate showed features of histiocytic necrotizing lymphadenopathy with proliferation of reactive large cells in a background of karyorrhectic debris and crescentic histiocytes, consistent with KFD. No fungus or acid-fast bacilli was identified (Figure 1).

Naproxen 500 mg BD, a non-steroidal anti-inflammatory drug, was initiated after the diagnosis of KFD. His fever subsided with reduction in cervical lymphadenopathy size and tenderness. He was subsequently discharged and was followed up for 1 year without development of other autoimmune diseases or recurrence of KFD.

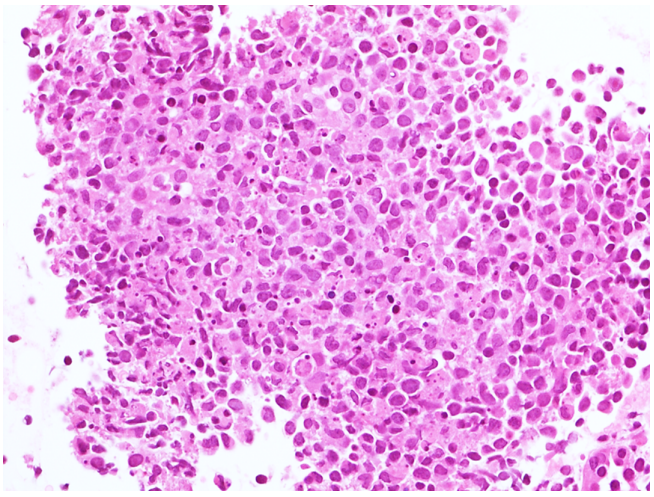

FIGURE 1 Histopathology slide of the fine needle aspirate of the right cervical lymph node showed features of histiocytic necrotizing lymphadenopathy with proliferation of reactive large cells in a background of karyorrhectic debris and crescentic histiocytes.

DISCUSSION

The exact prevalence of KFD is unknown but it was described as extremely rare in the pre-COVID-19 pandemic era.[1] On 12 March 2020, the World Health Organization declared a pandemic due to the worldwide transmission of SARS-CoV-2 and the significant number of fatalities resulting from COVID-19.[31] Vaccines aimed at combating the SARS-CoV-2 virus were swiftly created in response to the global pandemic, with over 13 billion doses administered globally.[32]

A literature search was conducted on PubMed and google scholar with keywords including Kikuchi, Fujimoto, COVID-19, and SARS-CoV-2. Since the start of the pandemic, 13 cases of post-COVID-19[5–17] KFD and 12 cases of post-COVID-19 vaccination[18–30] KFD have been reported worldwide. It has been suggested that SARS-CoV-2 can excessively stimulate the immune system, leading to generation of autoimmunity,[33] but the exact pathophysiological mechanism of post-COVID-19 KFD is still unknown. No causal link has been established between the COVID-19 vaccine and KFD either.[30] Our patient had a typical presentation of KFD with tender cervical lymphadenopathy and fever 1 month after recovering from COVID-19. This case contributes to the current body of knowledge regarding post COVID-19 KFD, potentially aiding future investigations into the pathophysiology and causal link between these two conditions.

When diagnosing KFD, there are no specific diagnostic criteria available. Histological examination is essential for the diagnosis of KFD, and more importantly, to exclude more serious conditions such as lymphoma, metastasis, or tuberculous adenitis.[34] Procedures used to obtain histological samples include excisional lymph node biopsy, fine-needle aspiration cytology (FNAC), and ultrasound-guided core biopsy.[35] In recent years, the primary diagnostic modality for KFD has been ultrasound-guided core needle biopsy, which has shown a diagnostic accuracy of 95.6%.[36] This procedure has become increasingly favoured over the previously recommended excisional biopsy for diagnostic purposes. Our case was diagnosed with ultrasound guided FNAC of the right cervical lymph node, which showed features of histiocytic necrotizing lymphadenopathy with proliferation of reactive large cells in a background of karyorrhectic debris and crescentic histiocytes, typical of KFD. However, literature have reported a lower diagnostic accuracy of 44.7% with FNAC, often attributed to tissue inadequacy.[36] At the end of the day, if cytologic findings from FNAC are compatible with a diagnosis of KFD, patients do not need to undergo open biopsy for confirmation.[35]

KFD typically follows a self-limiting course, as demonstrated in our case, with symptoms resolving spontaneously within 6 months.[2] Supportive measures, including the use of analgesics and antipyretics, are often employed. Patients with severe disease may be treated with corticosteroids. Out of the 13 reported cases of post-COVID-19 KFD, one case[9] was complicated by upper airway obstruction due to bilateral

cervical lymphadenopathy and required urgent tracheostomy with neck dissection. Corticosteroid was administered in two cases[9,10] while the rest of the 11 cases ran benign courses and were treated conservatively.[5–8,11–17]

In summary, we presented a case of KFD with a typical presentation of fever and cervical lymphadenopathy, diagnosed through ultrasound-guided FNAC, 1 month after COVID-19 recovery. This case serves as a reminder to clinicians and pathologists to consider KFD as a potential differential diagnosis in patients who exhibit cervical lymphadenopathy and fever following COVID-19 recovery or COVID-19 vaccination.

AUTHOR CONTRIBUTIONS

Cheuk Cheung Derek Leung, Hiu Ching Christy Chan and Ming Chiu Chan drafted the work. Yu Hong Chan, Man Ying Ho, Chun Hoi Chen and Ching Man Ngai reviewed it critically for important intellectual content. Yiu Cheong Yeung was in charge of final approval of the version to be published.

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CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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