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Kikuchi-Fujimoto Disease: A Case of Lymphadenitis Following COVID-19 Infection

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Abstract

Introduction: Kikuchi-Fujimoto disease (KFD), also known as histiocytic necrotizing lymphadenitis, is a rare disease of uncertain origin proposed to be secondary to viral or autoimmune causes. It presents as unilateral cervical lymphadenopathy and fever, typically resolving within a few months, however, it mimics malignant lymphoma, leading to extensive work-up fearing malignancy. **Case History:** A 33-year-old female with a history of Sjögren's syndrome, rheumatoid arthritis (not on immunosuppressive therapy) and recent COVID-19 infection two months ago presented with episodes of flu-like symptoms; fever (101˚F), chills, and myalgias for two months. Upon evaluation, she had leukopenia (WBC 1.8 k/uL), neutropenia (1.0 k/uL), elevated CRP (134 mg/L), and CT neck demonstrated multiple enlarged cervical lymph nodes with necrosis. The patient was started on Cefdinir and doxycycline for a possible atypical infection given neutropenic fevers and the patient continued to have fevers. A biopsy showed focal necrosis with no evidence of malignancy, suggesting KFD that was likely triggered by a recent COVID infection. She was treated with Prednisone and naproxen, which led to an improvement in symptoms and recovery of her pancytopenia. **Discussion:** This case is unique since the patient's recent infection with COVID-19 may have triggered the clinical manifestations of KFD. There have been a few case reports of children who were diagnosed with KFD after a COVID-19 infection and adults diagnosed with KFD following COVID vaccinations; however, this is the first case report involving a young adult in her thirties who was diagnosed with KFD two months after COVID-19.

Keywords

Kikuchi-Fujimoto Disease, COVID-19, Rheumatology

1. Introduction

Kikuchi-Fujmoto disease (KFD), also known as histiocytic necrotizing lymphadenitis, is a rare, self-limiting, lymphadenitis of uncertain etiology. [1] Patients typically present with cervical lymphadenopathy, with unilateral, tender lymph nodes that are usually in the posterior cervical triangle. Additional signs and symptoms can include non-specific clinical features such as fevers, chills, and weight loss. Patients can also present with widespread lymphadenopathy, fatigue, night sweats, nausea, vomiting, sore throat, or anorexia. [2] Many patients with KFD have leukopenia or neutropenia with a relative leukocytosis.

KFD is most commonly seen in Asia, however, recent cases have been reported in America, Africa, and Europe. [3] A majority of reported KFD cases have been in young women, typically of Asian descent. The disease is thought to have an autoimmune or infectious cause, with some patients developing KFD after infection with *Yersinia enterocolitica*, *Bartonella henselae*, or *Entamoeba histolytic*. [4] Viruses have also been suspected to be the inciting cause in some cases where patients developed KFD after infection with Epstein-Barr virus, Cytomegalovirus, or Parainfluenza virus. COVID-19 may also be a potential infection that may contribute to the development of KFD. [5] KFD itself is a self-limited lymphadenitis that typically resolves spontaneously in one to four months. It has an excellent prognosis and often does not cause any significant complications. Rarely, complications from KFD can include cardiac tamponade, pleural effusions, pulmonary infiltrates, thyroiditis, aseptic meningitis, meningoencephalitis, cerebellar ataxia, encephalitis with CNS lesions, or symmetrical polyarthritis. [6]

Since KFD presents with non-specific symptoms, there is often a broad differential physician have to keep in mind. Due to this, KFD has a misdiagnosis rate of approximately 40%. [7] Differential diagnoses include infectious causes, systemic lupus erythematosus (SLE)-related lymphadenopathy, and malignancy. In some cases, KFD can mimic B cell lymphoma, a malignancy with rapid growth. [8] Due to this, patients can often receive extensive workup and invasive testing, leading to unnecessary healthcare costs and worries for the patient.

Definitive diagnosis of KFD is typically done through a lymph node excisional biopsy. Histology typically shows paracortical foci of coagulative necrosis containing karyorrhectic debris. This is often surrounded by many histiocytes (stain positive for CD68/myeloperoxidase (MPO), plasmacytoid dendritic cells (stain positive for CD68/CD123), and some CD8+ lymphocytes.[1] An ultrasound can also be done of the lymph nodes, which would show a hypoechoic area with a thick, irregular hyperechoic ring around it. A CT scan or MRI can also be conducted, which shows enlarged lymph nodes with possible necrosis. [9]

Although KFD is a self-limiting condition, it mimics malignant lymphoma, and therefore an accurate diagnosis is crucial to prevent excessive workup and

healthcare burden. Furthermore, the etiology of KFD is still unknown, and may have an infectious or autoimmune component. In this manuscript, we present a rare case of a young female with a past medical history of Sjögren's syndrome and rheumatoid arthritis, who develops KFD following a COVID-19 infection.

2. Case History/Examination

A 33-year-old female with a history of Sjögren's syndrome, rheumatoid arthritis (not on immunosuppressive therapy), and recent COVID-19 infection two months ago presented with episodes of flu-like symptoms; fever of 101˚F, chills, and myalgias for two months.

The patient had upper respiratory symptoms consistent with influenza in October of 2022, for which she was given Tamiflu and had symptomatic improvement. The patient continued to have persistent myalgia and tested positive for COVID-19 in December of 2023. She had worsening congestion and ear pain, for which she was given a ten-day course of antibiotics. Despite completing antibiotics, the patient continued to have fevers and chills, prompting her to present to the Emergency Department.

During this visit, the patient presented with flu-like symptoms and had overall fatigue, generalized weakness, and myalgias. The patient's vitals on presentation to the Emergency Department were: Temperature 101.5˚F, BP 117/65, pulse 117, respiratory rate 18, SpO_2 100% on room air. On physical examination, the patient had non-tender cervical lymphadenopathy. All other physical examination findings were benign.

2.1. Methods

Her laboratory findings showed that she had leukopenia (WBC 1.8 k/uL), anemia (Hgb 10.6 g/dL), neutropenia (1.0 k/uL), thrombocytopenia (platelets 142 k/uL), elevated CRP (134 mg/L), AST (96 U/L), and ALT (83 U/L). She was started on Trimethoprim-Sulfamethoxazole and Oseltamivir. Despite this, the patient still had a fever of 101 - 102˚F, so the patient was admitted to the hospital for the management of neutropenic fever. She continued to have a fever over the next few days and was started on cefepime for empiric coverage. In consultation with infectious disease experts, extensive tests were ordered to find any potential infectious etiology, however, all workup was negative including CMV, EBV, HIV, and RPR. At this point, the antibiotics were switched to Cefdinir and Doxycycline, and additional imaging was completed.

A CT neck was completed which was remarkable for multiple enlarged cervical lymph nodes which were concerning for necrosis, as shown in **Figure 1**. As shown by the figure, there is a 13.5 mm enlargement of a cervical lymph node, with characteristics suggestive of necrosis. Due to the enlarged lymph nodes on physical exam as well as imaging, a core needle biopsy was conducted by Interventional Radiology. The biopsy showed paracortex necrosis.

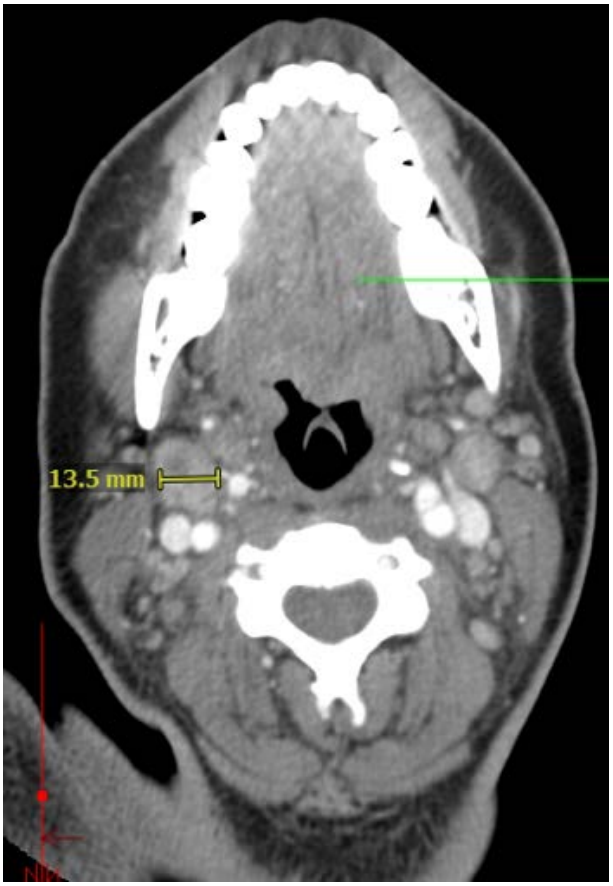

Figure 1. CT neck demonstrating multiple enlarged cervical lymph nodes concerning for necrosis.

2.2. Conclusion and Results

Her symptoms were hence consistent with KFD that was likely triggered by a recent COVID infection two months ago. She was treated with prednisone and naproxen, which led to an improvement in symptoms and recovery of her pancytopenia. The patient was discharged with a tapering course of prednisone with recommended outpatient follow-up. Since discharge, the patient has felt significantly better as she no longer felt the flu-like symptoms of fever, chills, and myalgias that she had originally presented with. This case underscores the importance of early and accurate diagnosis of KFD to avoid unnecessary procedures, healthcare costs, and patient anxiety associated with prolonged diagnostic workups.

3. Discussion

This case highlights a 33-year-old female with a past medical history of Sjögren's syndrome, rheumatoid arthritis, and a recent COVID-19 infection that was diagnosed with KFD. The patient presented to the emergency department with episodes of flu-like symptoms, a fever of 101˚F, chills, and myalgias for two months. The patient was started on Trimethoprim-Sulfamethoxazole and Osel-

tamivir, however, continued to be febrile, and was thus admitted to the hospital for neutropenic fever. A full workup was conducted to determine the cause of the patient's neutropenic fever and overall presentation, which eventually led to a head CT. Finally, a core needle biopsy was done due to enlarged lymph nodes on physical exam and imaging, which demonstrated that the patient had KFD. She was then treated with prednisone and naproxen, which improved her symptoms and resolved her pancytopenia. This case highlights the importance of early definitive diagnosis of KFD due to the additional procedures, healthcare costs, and patient distress that come with the excessive workup patients tend to receive. [6]

The two leading thoughts regarding the cause of KFD include an autoimmune origin or an infectious origin. Evidence supporting the autoimmune theory includes the increased incidence of KFD in patients with autoimmune conditions, specifically, SLE, Wegener granulomatosis, Sjögren syndrome, Graves disease, and Still disease. [1] Furthermore, there are also similarities in the endothelial cells and lymphocytes between KFD and other autoimmune conditions such as SLE on electron microscopy. There have also been case reports published of patients who were diagnosed with KFD and subsequently developed autoimmune conditions such as Sjogren's syndrome SLE/mixed connective tissue disease, suggesting a possible autoimmune origin. [10] In this case, the patient had a history of multiple underlying autoimmune conditions including Sjögren's syndrome and rheumatoid arthritis, further supporting the theory that autoimmune conditions factor into the pathophysiology of KFD.

The second leading theory for the development of KFD is caused by an underlying infection. There are many hypothesized agents that may predispose patients to developing KFD, ranging from viruses, to bacteria, to parasites. [2] Suspected agents include Epstein-Barr Virus, Human Herpes Virus 6 and 8, Human Immunodeficiency Virus, Herpes Simplex Virus, Hepatitis B, and Parainfluenza Viruses, along with the bacteria *Yersinia enterocolitica*, and the parasite *Toxoplasma gondii*; however, there has not been any study demonstrating a causal relationship between these infections and KFD. There has also been a rare case report where a 33-year-old male patient developed KFD shortly after being diagnosed with COVID-19 three months prior, and having a resolution of all COVID-19-related symptoms. [11] Our patient had a similar experience, when she was diagnosed with COVID-19 two months prior to her onset of new symptoms related to KFD, and she had been asymptomatic from her prior COVID-19 infection. Some experts believe it may be a combination of both the autoimmune and infectious theories, with KFD being a self-limited autoimmune disorder that can be triggered by viruses and other infectious agents. The patient presented in this case had both the history of autoimmune conditions, as well as a potential infectious trigger with the recent COVID-19 infection, suggesting that her condition may have developed from a combination of both of these different factors.

KFD is an important diagnosis to make since it often mimics malignancy. [12] The overall presentation of KFD can be variable, and since diagnosis requires biopsy, patients often receive many invasive tests during their initial work, and oftentimes do not receive a definitive diagnosis. Differentials for this disease typically include infectious causes, SLE, and malignancy, specifically B cell lymphoma. Due to KFD mimicking a potential malignancy that is rapidly progressive, significant invasive testing is often pursued. Overall, this leads to many unnecessary procedures and a great burden on the healthcare system. [13] This also takes a significant toll on a patient's mental health as the possibility of being diagnosed with cancer undoubtedly leads to substantial anxiety and worry among the patient and their loved ones. In addition, this also has a prominent effect on the patient's financial situation as they have to have multiple hospital visits, time off of work, as well as the costs of the procedures themselves. Our patient underwent multiple regimens of antibiotics, blood tests, and imaging, and finally, a biopsy to determine her diagnosis, all of which led to some distress in her life.

Despite mimicking malignancy and other chronic autoimmune conditions, KFD is typically a self-limited disease, with most patients recovering in approximately six months. [14] Treatment options can vary since KFD is often broadly treated with antibiotics as it mimics an infectious process, but patients typically also receive non-steroidal anti-inflammatory drugs (NSAIDs) and steroids. Oftentimes, KFD may also involve other organ systems, such as the heart, leading to perimyocarditis, however, these cases are also self-limiting and resolve completely with no residual deficits. [15] Although KFD itself may resolve completely, underlying autoimmune conditions that the patients may already have or may develop after the KFD diagnosis may require long-term medical treatment. [10] In this case, the patient recovered rapidly from the KFD, but still has chronic autoimmune conditions that she is being treated for, which has significantly impacted her quality of life.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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