Polish Annals of Medicine

Journal homepage: https://www.paom.pl

Review paper

Kikuchi-Fujimoto disease: State of the art

Katarzyna Lammek, Dmitry Tretiakow, Andrzej Skorek

Department of Otolaryngology, Medical University of Gdansk, Poland

ARTICLE INFO

Article history
Received 3 June 2020
Accepted 27 August 2020
Available online 7 June 2021

Keywords
Inflammation
Fever
Lymphadenopathy
Lymph node
Lymphatic system
Rare disease

Doi
https://doi.org/10.29089/2020.20.00161

ABSTRACT

Introduction: Kikuchi-Fujimoto disease (KFD), also called histiocytic necrotizing lymphadenitis, is a rare disease that occurs with swollen lymph nodes and associated fever. This disease occurs in both children and adults.

Aim: The aim of our work was to review the literature and to remind family doctors, otolaryngologists, hematologists and rheumatologists about this rare disease that should be included in the differential diagnosis of long-term cervical lymphadenopathy.

Material and methods: Current information on Kikuchi-Fujimoto disease was sought and presented based on literature that was published in reputable magazines in the period 2007–2020 in English. We searched for articles in the Medline, PubMed, and Scopus databases.

Results and discussion: KFD occurs in both children and adults. This disease is found all over the world, most often in the Asian population. The etiology of Kikuchi-Fujimoto disease is not entirely known, however, two causal theories are suspected, which are discussed in detail in our article. The course of the disease is mild and usually disappears on its own. A biopsy of an involved lymph node presented as the standard for diagnosis. KFD treatment was causal – nonsteroidal anti-inflammatory drugs and/or glucocorticosteroids were used.

Conclusions: There are few reports in the literature about Kikuchi-Fujimoto disease. KFD is associated with cervical lymphadenopathy and associated fever. If the diagnosis of the above-mentioned symptoms is not obvious, then in the differential diagnosis rarer diseases, such as KFD, should be included.

Corresponding author: Dmitry Tretiakow, Department of Otolaryngology, Medical University of Gdansk, Smoluchowskiego 17, 80-214 Gdańsk, Poland. Tel. +48 583 493 110; fax: +48 583 493 12.
E-mail address: d.tret@gumed.edu.pl.

1. INTRODUCTION

Many different diseases present with cervical lymph node enlargement and an accompanying fever: from inflammation of the upper respiratory tract, specific inflammatory changes, a complication of tonsillitis, nasal sinusitis, neck cysts to primary (e.g. lymphoma) and secondary neoplasms (e.g. metastases to lymph nodes).

It should also remember about systemic diseases, e.g. systemic lupus erythematosus (SLE), rheumatoid arthritis. It happens that the clinical picture of the disease is uncharacteristic for any of the commonly known disease entities, therefore it is difficult to properly and effectively help the patient. It is essential to make the correct diagnosis, which is the cause of long-term lymphadenopathy. Delay in the implementation of adequate therapy is associated with severe complications for the patient. If the diagnosis is not obvious, then you should think about less common diseases.

Kikuchi-Fujimoto disease (KFD), also called histiocytic necrotizing lymphadenitis, is a rare disease with unknown etiology. It belongs to a group of diseases called necrotic lymphadenitis.[1,2] KFD was first described in 1972 by two Japanese pathologists, Kikuchi and Fujimoto.[2,3] KFD is characterized by chronic cervical lymphadenopathy associated with fever. Most often, the course of KFD is mild and self-limiting. This disease occurs all over the world, however it is most often diagnosed in Asian countries. Therefore, the practicing physician should remember about KFD in patients with cervical lymphadenopathy, who have recently returned from a trip to Asia.[2,4,5] Due to the lack of pathognomonic clinical symptoms, about 40% of KFD cases are confused with other diseases involving lymphadenitis.[5]

2. AIM

We aimed to review the literature and remind family doctors, pediatricians, hematologists, rheumatologists, and otolaryngologists about this rare disease that should include in the differential diagnosis of long-term cervical lymphadenopathy.

2. MATERIAL AND METHODS

We sought literature on KFD published in journals from the Master Journal List in the period 2019–2020 in English. We searched for articles in the Medline, PubMed, and Scopus databases using the following keywords: 'Kikuchi-Fujimoto disease,' 'lymphadenopathy,' 'rare disease' and 'lymph node' (Figure 1). Inclusion criteria were: articles in English, meta-analysis, and review of the literature; individual case

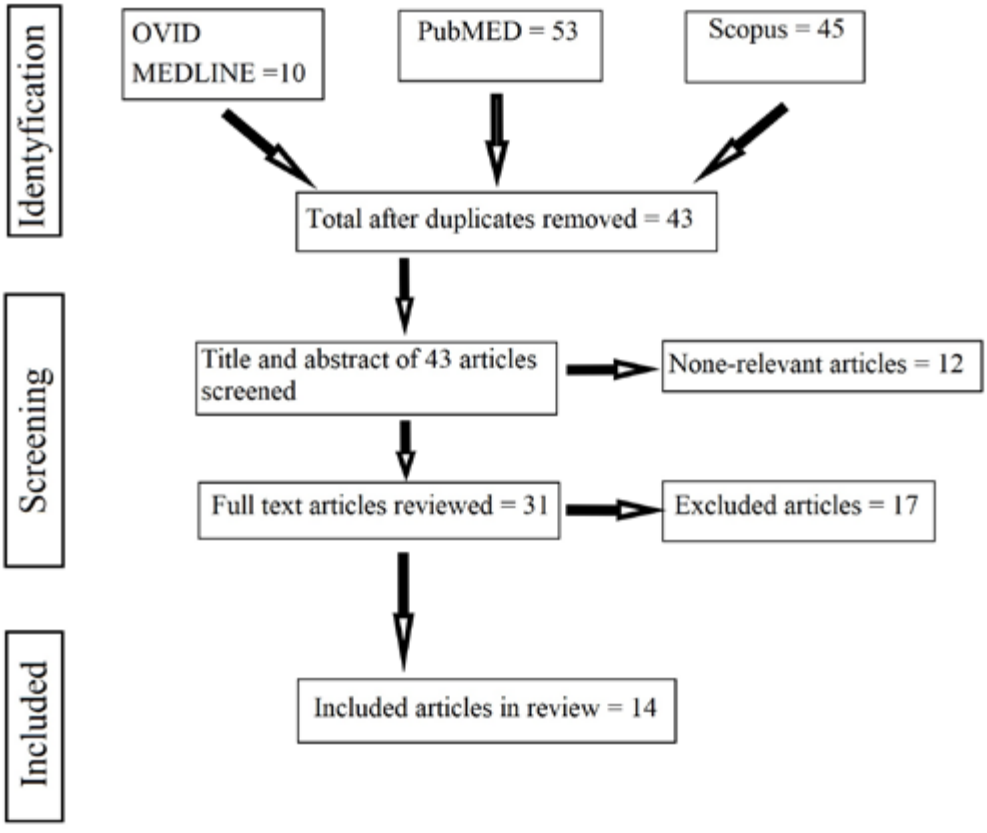

Figure 1. Flow diagram of the article search, identification and screening process.

reports that we found valuable in writing our article. Exclusion criteria were: articles in languages other than English excluded from the study; case report, apart from those that seemed very interesting and valuable for us in writing the publication.

3. RESULTS AND DISCUSSION

3.1. Etiology

The pathophysiology of KFD is not entirely known. However, two possible mechanisms were provided in the literature. The first is viral infection and the second theory explains the appearance of KFD in the course of autoimmune disease.[2,6,7]

The confirmation of the 'viral disease' theory in the course of KFD. The large number of histiocytes and $CD8^+$ lymphocytes in the affected lymph nodes seems to confirm the viral infection etiology of KFD. Patients with KFD were positive for parvovirus B19 and HHV-1, -3, -6, -7, -8 in polymerase chain reaction (PCR) studies. Other authors detected the sporadic presence of the HHV-2, -5, -6, -7 virus.[2]

According to the second theory, KFD is a manifestation of an autoimmune disease. This is based on the coexistence of KFD with autoimmune diseases, mainly SLE.[2] The symptoms of KFD (e.g. fever, fatigue, weight loss, lymphadenopathy and skin lesions) are similar to those of SLE. Some authors confirm the relationship between SLE and KFD.[2,3] However, the exact pathomechanism of the coexistence of these diseases is unknown. Jiménez-Heffernan et al. described a case of KFD in a patient with breast implants, suggesting that implants can initiate an inflammatory reaction that leads to the development of KFD.[7]

A rare cause of KFD is a skin infection caused by *Staphylococcus epidermidis*. The T-cell dysfunction or there excessive proliferation due to staph infection, by producing inflammatory cytokines, may play a role in the pathogenesis of KFD.[8]

3.2. Epidemiology and comorbidities

People of all ages suffer from KFD. However, the peak incidence falls on the 3rd and 4th decade of life. The occurrence of KFD in women is 3–4 times more frequent than in men, although recent studies show a gradual reduction of this disproportion (female to male ratio is 1.25–2.00 to 1.00).[3,4] In contrast, among children boys suffer from KFD slightly more often than girls (male to female ratio is 1.13 to 1.00).[4] The majority of KFD cases reported in the Asian population. There are individual reports of familiar occurrence of KFD.[3,5,9]

Autoimmune diseases, e.g., Still's disease, SLE, Hashimoto's disease, granulomatosis with vasculitis, are reported to co-occur with KFD. In most cases, Hashimoto's disease manifested itself at the same time as KFD.[3,6] KFD may co-occur before, during or after the onset of SLE. Therefore, the diagnosis of KFD requires longterm monitoring for the development of SLE. Kucukardali et al. reported that 13% of the general population, 9% of Europeans and 28% of Asians suffering KFD have SLE simultaneously.[10] It estimated that about 30% of KFD cases incorrectly diagnosed as lymphoma.[2]

3.3. Symptoms

The onset of KFD symptoms may be acute or subacute during 2 to 3 weeks. As mentioned earlier, the main symptoms of KFD are fever and cervical lymphadenopathy. Axillary or supraclavicular lymphadenopathy is rarely reported. In most cases, the enlarged lymph nodes have a diameter of less than 3 cm and sporadically reach a diameter of 5–6 cm. There may be intermittent or constant pain upon palpation of the affected lymph nodes. The fever is periodic, irregular, and oscillates between 38.6°C and 40.5°C.[2,7,11] Chills, nausea and vomiting, rash, headache and joint pain, weight loss, night sweats, splenomegaly, and parotid gland enlargement are other symptoms often found in KFD. Cutaneous symptoms appear in up to 40% of KFD cases, most often affecting the face, trunk, and upper limbs. Patients with KFD may have mouth ulcers, alopecia, erythema, swelling, sensitivity to sunlight, peeling skin, scabs, and swelling of the lips and eyelids. Erosions, nodules, and blisters meet less often. Skin lesions most often appear in the form of urticaria, purpura, papules resembling measles, rubella or a drug rash.[5,6] Symptoms of central nervous system involvement in KFD are rare and include encephalitis, meningitis, and cerebellar ataxia.[5,6,12] Individual cases of patients in whom KFD was manifested by optic neuritis were also reported in the literature.[9] In most cases, the course of the disease is mild. However, some patients develop severe symptoms associated with hemophagocytic lymphohistiocytosis (HLH). Both HLH and KFD are associated with abnormal activation of histiocytes.[2,4,11]

The duration of KFD is varied. Symptoms usually resolve within 6 months, however in individual cases, they can persist for up to a year. In a retrospective study of 43 patients with KFD, Marunaka et al. reported that the presence of a low percentage (less than 70%) of areas of the proliferation of immature histiocytes in the enlarged lymph node and the lack of atypical lymphocytes in the peripheral blood were associated with a longer duration of the disease. However, this theory requires confirmation in more randomized studies.[13]

3.4. Diagnostics

There is no specific laboratory test confirming KFD. Blood tests show some deviations from the norm, i.e., anemia, leukopenia, leukocytosis. Elevated levels of LDH, OB, CRP, and transaminases were reported. Leukopenia was found in 25%–58% of patients and leukocytosis in about 2%–5% of patients with KFD.[2,6] However, according to some authors the results of laboratory tests in patients with KFD may not show abnormalities.[3]

X-ray, CT or MRI examinations were performed to exclude other causes of lymphadenopathy, e.g., specific inflammation, lymphoma, or cancer metastasis.[1,3,10] However, the final diagnosis is based on the result of histological examination of biopsy samples from an enlarged lymph node.[10]

There are three histological patterns of KFD: proliferative, necrotizing, and xanthomatous.[3,10,14] The microscopic picture of KFD in its proliferative phase is very similar to anaplastic lymphoma and Hodgkin's lymphoma. It is due to the presence of large immunoblasts with a pleomorphic, follicular nucleus and visible nucleolus. The histological structure of the lymph node is partially preserved. The histologically characteristic features of KFD: the presence of necrosis with a concentration of apoptotic cells in the central part of the lymph node; lack of neutrophils and eosinophils; occurrence on the periphery histiocytes, active lymphocytes, and plasmatic dendritic cells.[1,3,14]

The histological structure of the nodes in KFD is similar to mononucleosis, tuberculosis, lymphoma, and SLE. However, there are visible differences in the histological structure, which allows distinguishing KFD from those diseases, as mentioned above. Necrosis is not as severe in lymphoma as KFD. Moreover, granulomatous infiltrates are usually absent. The presence of hematoxylin bodies is found in SLE, i.e., molecules of denatured nuclear material, the Azzopardi phenomenon – the presence of DNA in necrotic blood vessels, a large number of plasma cells and a few $CD8^+$ T lymphocytes. The use of immunohistochemical staining shows a large number of $CD8^+$ lymphocytes and $CD68^+$ histiocytes. The $CD20^+$ cells were founded in diffuse large B-cell lymphoma. The characteristic histiocytes, which usually produce myeloperoxidase and $CD68^+$, $CD163^+$ and $CD4^+$ are found in KFD.[2,5,6]

In several studies on patients with KFD and silicone breast implants, it has been shown that in diagnostics, it is possible to perform a fine needle biopsy with the collection of serous fluid accumulating around the breast implant to diagnose KFD. Cytological features of the serous fluid were similar to those found in the enlarged lymph nodes of patients with KFD. The presence of reactive lymphocytes, the remains of disintegrated cell nuclei, histiocytes with a crescent nucleus, and the lack of neutrophils can be indicative of a non-node KFD-type reaction. Also, histiocytes with a crescent nucleus and intracellular apoptotic debris were present. These cells are much smaller than macrophages and are characteristic of KFD.[7]

Autoimmune diseases (e.g., SLE, Kawasaki disease, sarcoidosis), congenital disorders (e.g., lingual-thyroid cyst, dermoid cyst, and pharyngeal clefts) and infectious diseases should be include in the differential diagnosis of KFD.[2,4,6,11] Epstein-Barr virus, cytomegalovirus, HIV, rhino-, adenovirus and rubella virus infection were mentioned among the viral causes of lymphadenopathy.[2] *Staphylococcus aureus* and *Streptococcus pyogenes* are the most common causes of purulent lymphadenitis.[2] Differential diagnosis of KFD should also include cat-scratch disease, toxoplasmosis or nodal form of tuberculosis.[2,3]

3.5. Treatment

KFD is, in most cases, a self-limiting disease. In cases where the disease has not resolved spontaneously, a symptomatic treatment should be offered.[2,3,5,9]

Non-steroidal anti-inflammatory and analgesic drugs should use in pharmacological treatment. Glucocorticosteroids are used in severe cases, but the exact dose and duration of treatment should be individually-tailored. Dosages of glucocorticosteroids range 30–60 mg per day for 3–5 days, with a decreasing dose for 7–10 days. Hydroxychloroquine is an additional medicine used to treat KFD.[2] There are reports in the literature of the efficacy of the combination of prednisolone with hydroxychloroquine in the induction of KFD remission.[3] In cases KFD extending from optic neuritis, glucocorticoids and rituximab was used with good therapeutic effect.[9] It has shown that antibiotic therapy KFD is ineffective. However, they are often used to avoid the potential superinfection lymph node.[5] It recommends that the KFD patients should be monitored for several years annually for SLE because of the frequent coexistence of these diseases.[3]

4. CONCLUSIONS

KFD is a mild, self-limiting disease. It occurs most often in the 3rd and 4th decade of life, most often in women. The etiology of the disease is unknown. It suspected that the cause might be a viral or autoimmune disease. Common symptoms include fever and cervical lymphadenopathy. The standard management for differential diagnosis is involved in lymph node biopsy, blood tests, and imaging tests. KFD should differentiate from other disease entities in which lymph node involvement occurs. Treatment depends on the severity of the case. Non-steroidal anti-inflammatory drugs and glucocorticosteroids should be administer.

Conflict of interest

The authors declare no potential conflicts of interest concerning the authorship and publication of this article.

Funding

This work not supported in any foundation.

References

1 Nair I, Balan S, Phalak P, Daniel M. Clinicopathologic spectrum of necrotizing lymphadenitis. *Indian J Pathol Microbiol*. 2020;2020;63(1):60–63. https://doi.org/10.4103/ijpm.ijpm_622_19.

2 Singh JM, Shermetaro CB. Kikuchi-Fujimoto disease in Michigan: A rare case report and review of the literature. *Clin Med Insights Ear Nose Throat*. 2019;12:1179550619828680. https://doi.org/10.1177/1179550619828680.

3 Salamat S, Chan J, Jolly K, et al. Kikuchi–Fujimoto Disease and prognostic implications. *Head Neck Pathol*. 2020;14(1):272–275. https://doi.org/10.1007/s12105-019-01026-0.

4 Selvanathan SN, Suhumaran S, Sahu VK, Chong CY, Tan NWH, Thoon KC. Kikuchi-Fujimoto disease in children. *J Paediatr Child Health*. 2020;56(3):389–393. https://doi.org/10.1111/jpc.14628.

5 Xu S, Sun W, Liu J. Kikuchi-Fujimoto disease: A case report and the evaluation of diagnostic procedures. *BMC Oral Health*. 2019;19(1):223. https://doi.org/10.1186/s12903-019-0920-4.

6 Sharma K, Otieno F, Shah R. Case report of Kikuchi-Fujimoto disease from Sub-Saharan Africa: An important mimic of tuberculous lymphadenitis. *Case Rep Med*. 2020;2020:4385286. https://doi.org/10.1155/2020/4385286

7 Jiménez-Heffernan JA, Muñoz-Hernández P, Bárcena C. Kikuchi-Fujimoto disease-like inflammatory reaction in a silicone breast implant seroma. *Acta Cytol*. 2020;64(4):386–389. https://doi.org/10.1159/000505253.

8 Cao NT, Nguyen HT, Pham VHT, et al. Reactive hemophagocytic lymphohistiocytosis-associated Kikuchi-Fujimoto disease after a Staphylococcus epidermidis cutaneous infection. *JCR J Clin Rheumato*l. 2019;27(3):e96–e97. https://doi.org/10.1097/RHU.0000000000001279.

9 Arslan A, Kraus CL, Izbudak I. Optic neuritis as an isolated presentation of Kikuchi–Fujimoto disease in a pediatric patient. *Balkan Med J*. 2020;12;37(3):172–173. https://doi.org/10.4274/balkanmedj.galenos.2019.2019.11.88.

10 Moyer A, Hanafi ZM, Scordino T, Bronze M. Kikuchi-Fujimoto disease: An atypical presentation of a rare disease. *Cureus*. 2019;11(2):e3999. https://doi.org/10.7759/cureus.3999.

11 Ahn SS, Lee B, Kim D, et al. Evaluation of macrophage activation syndrome in hospitalised patients with Kikuchi-Fujimoto disease based on the 2016 EULAR/ACR/PRINTO classification criteria. *PLoS One*. 2019;18;14(7):e0219970. https://dx.plos.org/10.1371/journal.pone.0219970.

12 Shabana M, Warnack W. An atypical neurologic complication of Kikuchi-Fujimoto disease. *Neurol Neuroimmunol Neuroinflamm*. 2020;16;7(3):e707. https://doi.org/10.1212/NXI.0000000000000707.

13 Marunaka H, Orita Y, Tachibana T, et al. Kikuchi-Fujimoto disease: Evaluation of prognostic factors and analysis of pathologic findings. *Acta Oto-Laryngologica*. 2016;136(9):944–947. https://doi.org/10.3109/00016489.2016.1164895

14 Sukswai N, Jung HR, Amr SS, et al. Immunopathology of Kikuchi-Fujimoto Disease: A reappraisal using novel immunohistochemistry combinations. *Histopathology*. 2019;77(2):262–274. https://doi.org/10.1111/his.14050.