

REVIEW

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## Kikuchi Fujimoto Disease

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**Abstract:** In order to determine the clinical significance of Kikuchi Fujimoto Disease (histiocytic necrotizing lymphadenitis) and to review the literature available on this condition, we selected the Medicine research papers in English language published between the years 1972 to 2011.

Kikuchi Fujimoto Disease (KFD) is an uncommon, cosmopolitan, benign and self-limiting condition with higher Japanese and Asian prevalence. Most of the sufferers of KFD are young people who seek treatment because of having acute tender cervical lymphadenopathy, low grade fever and night sweats. Coagulative necrosis with ample karyorrhetic debris in paracortical areas of the involved lymph nodes is the characteristic histologic feature of KFD. Diagnosing KFD is crucial as it can be mistaken for malignant lymphoma and SLE.

KFD was put forth first time in 1972 by Dr. Masahiro Kikuchi and by Fujimoto as lymphadenitis with reticular proliferation, histiocytes and abundant nuclear debris. It is a rare benign condition of lymph nodes and most of the clinicians and pathologists are unfamiliar with it. KFD is self-limiting disease (within 1 to 4 months), however, patients should be followed up regularly as it may crop up again or progress to SLE. Analgesics and antipyretics help to ameliorate the symptoms.

**Keywords:** Kikuchi, Kikuchi Fujimoto Disease, KFD, histiocytic necrotizing lymphadenitis, SLE, malignant lymphoma

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## Literature Review

We collected all possible literature from the year 1972 (when KFD was first described) to the present day conducting a medical search on Kikuchi Fujimoto Disease (KFD) in English language. We included publications in authorized medical journals including original and review articles/theses, editorials, case reports and brief communications.

## Epidemiology

KFD is an extremely uncommon disease but cosmopolitan with higher Japanese and Asiatic prevalence.<sup>1,2</sup> However, sporadic cases have also been reported from Europe. In Asian woman Kikuchi's Disease is rare and benign cause of cervical lymphadenopathy.<sup>3</sup> The disease, most often, happens to occur in young adults below 40 and seldom in children.<sup>4</sup> At first, little female predominance was considered, but the recent literature regards it as male to female ratio 1:1.<sup>1,5</sup> A current study on the patients with KFD conducted in Taiwan reports the average age of 21.<sup>5</sup> Cardiac, hepatic and pulmonary involvement raises the morbidity. SLE is another fatality associated with Kikuchi Fujimoto Disease.<sup>6</sup>

## Etiology and Pathogenesis

The exact etiology of Kikuchi's Disease is still unknown. The recent literature is inclined to viral or autoimmune causes. However, role of viruses (Epstein-Barr virus and others) in the pathogenesis of Kikuchi's Disease is controversial and unremarked.<sup>1</sup> On the other hand, Unger and coworkers are in favor of viral etiology as KFD manifests certain viral features ie, atypical lymphocytosis, certain histologic features, flulike respiratory prodrome and no response to antibiotic therapy.<sup>7</sup> Also, Kikuchi's Disease has been reported in patients with AIDS.<sup>8</sup>

Like systemic lupus erythematosus (SLE), lymphocytes and histiocytes in the patients with Kikuchi's Disease show tubular reticular structures in their cytoplasm on electron microscopy.<sup>9</sup> It has been opinioned that in genetically susceptible individuals, KFD may belong to exuberant T-cell mediated immune response provoked by variety of stimuli.<sup>1</sup> Even though course of cell death in KFD needs to be studied and emphasized, Ohshima and his associates remarked apoptotic cell death might be involved in

the pathogenesis of KFD.<sup>10</sup> Regarding to this study, proliferating CD8 T-cells may kill or be killed in the apoptotic process of this disease using Fas and perforine pathways.

## Clinical Manifestations

Kikuchi's Disease begins as an acute or sub-acute condition, developing over two to three week period. Tender cervical lymphadenopathy is the characteristic feature (56%–98%) of KFD, predominantly involving the posterior cervical triangle. Size of the enlarged lymph nodes ranges from 0.5 cm to 4 cm (occasionally 6 cm). 59% patients represent painful lymphadenopathy and 1%–22% patients undergo generalized lymphadenopathy.<sup>4,7,9,11</sup> KFD, more or less, rarely involves mediastinal, peritoneal or retroperitoneal regions of the body.<sup>2</sup>

Fever (30%–50%) associated with upper respiratory symptoms, sore throat, night sweats, weight loss, headache, rash, nausea, vomiting, and leukopenia (about 50%) are the other manifestations of the disease.<sup>12,13</sup> Atypical lymphocytes have been reported in the peripheral blood film of patients with KFD. Extranodal involvement is rare; however, skin, eye and bone marrow affection has been reported.<sup>1</sup> Nevertheless, KFD is linked to SLE and autoimmune conditions as lymphocytes and histiocytes in the patients with Kikuchi's Disease show tubular reticular structures in their cytoplasm on electron microscopy.<sup>1,14</sup>

Additionally, extranodal involvement in KFD is associated with frequent systemic symptoms. Anecdotal reports bring to light the unusual features of KFD like haemophagocytic syndrome and carcinoma<sup>15</sup> along with fatal multicentric disease. Nervous system involvement (septic meningitis, acute cerebellar ataxia, and encephalitis) rarely happens to occur.<sup>16</sup> Regarding joint involvement, a case of 14 year old boy with KFD is in the record.<sup>17</sup>

## Diagnosis

In patients with Kikuchi Fujimoto Disease, an excisional biopsy of the involved lymph nodes is the investigation of choice. Coagulative necrosis with ample karyorrhetic debris in paracortical areas of the involved lymph nodes is the characteristic histologic feature of KFD. Other baseline investigations are



reported unaffected. Nevertheless, laboratory results of some KFD cases have reported anemia, little rise in ESR and even leukopenia. One third individuals with KFD have shown atypical lymphocytes in their peripheral blood films.<sup>5</sup> Predominantly, T-cells (CD8+ T-cells) are found in KFD. However, neutrophils are found absent and scarce plasma cells may or may not be present.

According to Kuo, histopathologic features can be classified in three stages: proliferative, necrotizing, and xanthomatous.<sup>18</sup> Proliferative stage expresses various histiocytes, plasmacytoid monocytes and lymphoid cells containing karyorrhetic nuclear fragments, and eosinophilic apoptotic debris. Necrotizing stage shows a degree of coagulative necrosis while xanthomatous stage is predominantly stuffed with foamy histiocytes.

It must be born in mind that in the individuals with KFD, atypical reactive immunoblastic component is common and can be mistaken for lymphoma.<sup>4</sup> Histiocyte-associated antigens (lysozyme, myeloperoxidase and CD68) are also expressed by histiocytes in KFD.

## Differential Diagnosis

KFD is an extremely rare disease and the differential diagnosis can be established on the basis of enlarged lymph nodes which are associated with many other disorders. It is necessary to born in mind the differential diagnosis of KFD as its treatment dramatically differs from other disorders. Lymphoma (non-Hodgkin's lymphoma), tuberculosis, SLE, plasmacytoid T-cell leukemia, Kawasaki's disease, and myeloid tumor are included in the differential diagnosis of KFD.<sup>1</sup>

Sometimes, because of similar clinical and histological features, it becomes problematic to differentiate Kikuchi Fujimoto Disease from lymphadenitis associated with systemic Lupus erythematosus (SLE). However, it has been reported that KFD is associated with SLE. In order to exclude SLE, all the necessary investigations of SLE (C3, C4, ANF, anti-Sm, and LE cells) are required. Early recognition of Kikuchi Fujimoto Disease is of prime importance to save the patient from undergoing extensive investigations related to malignant lymphoma and other related disorders.<sup>8</sup> Histopathologic features like presence

of abundant reactive histiocytes and absence of Reed-Sternberg cells favor KFD.

Sometimes, KFD may express histiocytes resembling with signet-ring cells and can be confused with signet-ring carcinoma. However, metastatic adenocarcinoma contains cells with atypical nuclei and mucin debris instead of cellular debris.

## Management

Kikuchi Fujimoto Disease (histiocytic necrotizing lymphadenitis) is a self-limiting condition that resolves spontaneously within 1 to 4 months of period. However, studies reveal recurrence of the disease in 3%–4% of the patients.<sup>9</sup> Additionally, SLE may happen to occur some years later. No hereditary risk has been documented in KFD.<sup>8</sup> Most of the time symptomatic relief is offered for the local and systemic complains of the disease. Lymph node tenderness and fever is treated with analgesics, antipyretics, and NSAIDs. Sometimes, but rarely, steroids can be used temporarily, especially in severe extranodal involvement or generalized clinical course.<sup>19</sup> In order to run an excisional biopsy of the enlarged lymph nodes, surgical consultation may be prerequisite.

Individuals with Kikuchi Fujimoto Disease should be examined systemically and they must be under regular follow-up in order to monitor the manifestations of SLE. The course of cervical lymphadenopathy is benign and resolves spontaneously. Very few cases have been reported as fatal. However, no standard or specific treatment of KFD has been recommended.

## Conclusion

Kikuchi Fujimoto Disease is an idiopathic, extremely rare, more or less worldwide, and often underdiagnosed condition; predominantly involving the posterior cervical lymph nodes. Kikuchi's disease seems to be more prevalent in Japanese and Asian individuals. KFD has an excellent prognosis with little risk of fatality. Histopathologic features support its cause being viral. Early recognition of Kikuchi's Disease is of prime importance to avoid extensive and expensive investigations related to malignant lymphoma other related disorders. In order to avoid misdiagnosis, awareness of this disease is necessary for the clinician as well as for the pathologist. KFD



should be considered in young patients with nodal biopsy showing necrosis and karyorrhexis.

## Author Contributions

Conceived and designed the experiments: JA. Analyzed the data: JA. Wrote the first draft of the manuscript: JA. Contributed to the writing of the manuscript: JA. Agree with manuscript results and conclusions: JA. Jointly developed the structure and arguments for the paper: JA. Made critical revisions and approved final version: JA. All authors reviewed and approved of the final manuscript.

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