State of the Globe: Time to Revisit Kikuchi Fujimoto Disease

Kikuchi-Fujimoto disease (KFD) is a rare and unusual condition, presenting in patients younger than 40 years of age, as a benign, self-limiting condition, characterized by cervical lymphadenopathy, fever, and joint pain.[1] A small percentage of patients may develop flu-like symptoms, skin rash, hepatitis, arthritis, and oral ulcers.[2,3]

The cause of KFD is not completely known, however, certain infectious agents (Epstein-Barr virus (EBV), *Yesinia*, herpes virus 6 and 8, *Toxoplasma*, parvovirus B19, *Brucella*, human immunodeficiency virus) and the genetic deficiency of the human leukocyte antigen (HLA) class II are frequently associated with its incidence.[4,5] Some studies have linked the higher prevalence of KFD in the Asian population with the deficiency of *human leukocyte antigen (HLA) Class II* genes such as the DPA1*01 allele and DPB10202 allele, which are commonly seen in the Asian population.[3,6] A recent study of 88 patients with KFD, in the US, showed that nearly 75% of the patients were Caucasians, which showed that the disease might not be predominantly seen in the Asian population.[7]

Kikuchi-Fujimoto disease was initially reported to be more common in females, but recent studies have shown that the distribution is almost equal in both the sexes.[3,6] Clinically, KFD is often misdiagnosed with systemic lupus erythematosus (SLE), malignant lymphoma or early stage tuberculosis.[3,5,8] The commonly affected site for lymphadenopathy in the neck is usually in the cervical area and is associated with tenderness.[7] The size of the lymph nodes varies from 0.5 cm to 8 cm. On rare occasions, lymphadenopathy can be generalized and involves the mediastinal, peritoneal, and retroperitoneal regions.[2,4,9] Neurological involvement can be seen in KFD, presenting as aseptic meningitis, brachial neuritis, mononeuritis multiplex or hemiparesis. In rare instances, rapid progressive cerebellar ataxia, disseminated encephalomyelitis, and peripheral neuropathy may create a diagnostic challenge.[10-12]

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The characteristic histopathological features from lymph node biopsy help in distinguishing it from other conditions. The histopathological findings on biopsy show patchy necrosis in the cortical and paracortical areas of the lymph node, together with nuclear debris or extensive karyorrhexis. Cellular infiltration consists of CD68-positive plasmacytoid histiocytes and transformed lymphocytes, which largely originate from T-cells. In a majority of the cases, there is an absence of neutrophils, eosinophils, and plasma cells.[2,4,6,13,14] CD8-positive T cell-mediated apoptotic cell death has been postulated as the principal mechanism of cellular destruction.[14] In a study of four men with biopsy-confirmed KFD, interferon gamma and interleukin-6 were seen to be elevated in the acute phase of the illness.[15] Although specific diagnostic tests are not available for diagnosing KFD, an analysis of the serology titers for the commonly associated infectious agents is always helpful, for narrowing the diagnosis.[5] KFD also shares the histological features with SLE, with both the conditions presenting, with tubuloreticular structures in the lymphocytes and endothelial cells.[16]

The laboratory tests are consistent with non-specific signs of underlying inflammation. Leukopenia, atypical lymphocytosis, and thrombocytopenia are more frequently associated with other derangements. The erythrocyte sedimentation rate elevation to more than 60 mm/hour has been associated with nearly a third of the patients. Bone marrow studies can reveal an increase in macrophages without atypical cells.[7,17] Computed tomography (CT) imaging of the involved lymph nodes shows peripheral infiltration and homogenous contrast enhancement. These are often mistaken as signs consistent with a malignancy.[18,19]

As the signs and symptoms of KFD are consistent with an underlying inflammatory response, trials with high-dose glucocorticoids with intravenous immunoglobulins have shown improvement in a majority of patients with severe and persistent symptoms.[20,21] Symptomatic management of other systemic symptoms provides temporary relief, without affecting the duration of the illness. Although KFD is a self-limiting condition, recurrences have been reported in some studies. In a series of 102 patients from Korea, it has been shown that three patients developed SLE, eight patients had an early relapse, and 13 patients had a late recurrence of the disease.[22]

As there are no confirmatory laboratory tests for diagnosing KFD, comprehensive evaluation, histopathological examination, and careful correlation with laboratory findings makes it imperative to think of KFD as a differential diagnosis in patients presenting with cervical lymphadenopathy and fever. The study conducted by Rakesh *et al.* has presented an exhaustive review, with results that are consistent with the previously published literature on the presentation and management of KFD. Future studies on KFD should be targeted toward generating a correlation between various clinical features and outcomes. This could provide a significant change in medical practice by augmenting the ability to assess disease severity and prepare the healthcare providers for managing rare complications associated with the disease. Studies evaluating treatment responses and tailoring them to early relapse and late recurrence will also provide further insight toward the outcome of patients with KFD.

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