Rare presentation of Kikuchi Fujimoto Disease with Thrombocytopenia - case report and review of literature

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Abstract
Kikuchi-Fujimoto Disease is a rare benign, condition of necrotising histiocytic lymphadenitis. The importance of this disease is that it is an uncommon differential for lymphadenopathy. Non-Hodgkin lymphoma (NHL), systemic lupus erythematosus (SLE) and other granulomatous conditions should be ruled out with the use of ancillary studies prior to the diagnosis of Kikuchi-Fujimoto disease, due to overlapping clinical and histologic features as well as the different therapeutic approaches. A case of a 45 year old female is described here. Of significant note, this patient developed significant thrombocytopenia which is a rare occurrence with Kikuchi’s disease.

Introduction
Kikuchi or Kikuchi-Fujimoto disease (KFD) or Histiocytic necrotizing lymphadenitis (HNL) is an enigmatic, benign cause of regional lymphadenopathy, which is usually accompanied by mild fever, night sweats and tenderness of the lymph nodes. It was initially described by, Kikuchi [1] and then by Fujimoto and associates [2] in Japan in 1972. However, most of the clinicians’ and pathologists are still unfamiliar with this entity. It is a rare cause of lymphadenopathy with a predilection for cervical lymphadenopathy. The diagnosis of KFD is established by identifying characteristic histopathological features. However, diagnosis requires histopathological examination and exclusion of other diseases with overlapping clinical and histopathological factors such as Non-Hodgkin lymphoma (NHL), systemic lupus erythematosus (SLE) and other granulomatous conditions.

Kikuchi’s disease is typically reported to have a self-limiting course, resolving within several months of diagnosis, further it has a low recurrence rate ranging from three to four percent [3]. There is no specific treatment for KFD but any treatment is generally directed towards symptomatic relief. In severe cases, corticosteroids have been used without relapse of the disease.

We report a case of Kikuchi’s lymphadenitis with associated thrombocytopenia

Case report
A 45 year old female presented to the local hospital reporting tender, slow-growing, right sided sub mandibular swelling (Figure 1), associated with malaise, weight loss and intermittent low-grade fever at night for a period of five months. Examination revealed mild hepatomegaly. Hematological investigations were inconclusive except for a platelet count of 48,000 /μL.

The ultra sound scan (USS) of neck, reported
multiple enlarged nodes along carotid vessels on right side, level two (largest measuring two centimeters in diameter), and Sub mandibular region (largest measuring three centimeters in diameter). Multiple posterior auricular and pre-auricular lymph nodes were also positive. However, central fatty hilum was not visible in most mattered nodes with no central caseation. Fine needle aspiration cytology (FNAC) and the chest x-ray were inconclusive.

Even though the patient was asymptomatic due to persistent thrombocytopenia, a bone marrow aspirates and trephine was performed, which was normal. As she was awaiting surgery for lymph node biopsy apheresis platelets were transfused to optimize the platelet count of 10,000/μL. Following transfusion of she developed a reaction and the post transfusion platelet count was 5000/μL. Therefore the surgery was postponed and patient was started on oral steroids with a daily dose of 1mg/kg and she improved quickly.

The excisional biopsy was performed and the specimens sent for Acid fast test and the histopathological analysis reported necrotic lymph node with evidence of multifocal necrotic zones with karyorrhectic debris. These histopathological features were suggestive of Kikuchi’s lymphadenitis. Currently she’s being closely followed up in the Oral and Maxillofacial clinic for any recurrences, for development of any auto immune conditions such as SLE or thrombocytopenia.

Discussion
Lymph nodes are considered to be the fortress that aid immune system. The causes of lymphadenopathy or swollen / enlarged lymph nodes could be due to the following reasons infections, immunologic disorders malignancies, lipid storage diseases, and miscellaneous causes such as Sarcoidosis, Kikuchi’s disease and Kawasaki’s disease [4]. However, KFD is one of the rare causes of cervical lymphadenopathy and known to have a worldwide distribution with a higher prevalence among Japanese and other Asian people [5]. A female preponderance is reported (female to male ratio of four to one) [5]. Although the affected patients are most often adults younger than 40 years, the disease is seldom reported in children. A recent series from Taiwan of 61 patients with KFD revealed a mean age of 21 Years [5].

There is much speculation about the aetiology of KFD; a viral or autoimmune cause has been suggested. In this presented case the negative results for most of the investigations were compatible with a study done by Dorfman [6] which also showed similar results.

Therefore, in this case also as by the literature possible aetiology was inconclusive. However, some initial reports hinted at Yersinia enterocolitica and Toxoplasma gondii as possible causative agents of KFD, mainly on the basis of positive serologic test results but, subsequent studies failed to support these hypotheses [7]. Further, the role of Epstein - Barr virus and other viruses (HHV6, HHV8, parvovirus B19) in the pathogenesis of KFD remains controversial and is not convincingly demonstrated [5].

The onset of KFD is acute or subacute, evolving over a period of two to three weeks. Involvement of cervical lymphadenopathy is present in 56% to 98% of cases with predilection to the posterior cervical triangle (88.5%). Generalized lymphadenopathy has been reported in one to twenty two percent of cases, but the involvement of mediastinal, peritoneal, and retroperitoneal regions is uncommon [5]. Lymph node size ranges from one to four centimeters (93.4%) and rarely larger than six centimeters. In addition to lymphadenopathy, 30% to 50% of patients with KFD might have fever, usually low-grade, associated with upper respiratory symptoms. Less frequent symptoms include weight loss,
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nausea, vomiting, sore throat, night sweats and hepatosplenomegaly [8]. It has been noted that systemic symptoms are found more frequently when extranodal involvement is present [6].

Some authors have reported anaemia, leukopenia, and recurrent thrombocytopenia [9]. Even though her ESR and CRP were within normal limits, increase CRP, serum lactate dehydrogenase [5] and slight elevation of the ESR has been reported. According to Dorfman [6] mild leukopenia has been observed in 25% to 58% of patients, leukocytosis in two to five percent of cases and 25% to 31% of patients had atypical peripheral blood lymphocytes, which might support the aforementioned speculated viral cause.

Unfortunately, this disorder does not have a characteristic appearance on ultrasonography or computed tomographic (CT) examination. The findings of CT and magnetic resonance imaging of KFD can be variable and mimic not only lymphoma but also various nodal diseases with necrosis, including metastasis and tuberculosis [10]. The overall diagnostic accuracy of FNAC for KFD has been estimated at 56.3% [11]. As diagnosis of KFD is on the basis of an excisional biopsy of the affected lymph nodes, excisional lymph node biopsy is mandatory if clear-cut clinical and cytological KFD findings are absent.

The diagnosis of KFD is performed by the architectural features and the characteristic cytological composition of lymph node biopsy specimens. These characteristic histopathologic findings are irregular paracortical areas of coagulative necrosis with abundant karyorrhectic debris (Figure 2a), which can distort the nodal architecture, and large number of different types of histiocytes at the margin of the necrotic areas. The karyorrhectic foci are formed by different cellular types, predominantly histiocytes and plasmacytoid monocytes but also immunoblasts and small and large lymphocytes. Neutrophils are characteristically absent and plasma cells

Figure 1. This shows the fullness in right side submandibular region (Arrowhead) with the visible scar which resulted from the previous excisional biopsy.

Figure 2a. H & E stains demonstrating necrotic areas. (Magnification 10x20)

Figure 2b. H & E stains demonstrating the lymphoid tissue. (Magnification 10x20)
are either absent or scarce [12, 13]. Importantly, atypia in the reactive immunoblastic component is not uncommon and can be mistaken for lymphoma when a proliferation of plasmacytoid monocytes, immunoblasts, and small lymphocytes is seen without necrosis [12] (Figure 2b). Sometimes the karyorrhectic process scan extends beyond the nodal capsule and into perinodal tissue [5]. In line with these findings our patient also showed necrotic lymph nodes with evidence of multifocal necrotic zones with karyorrhectic debris. Even though Grocott and acid fast stains failed to reveal organisms the possibility of Tuberculosis was not completely excluded and she was further investigated.

Kuo et al. [14] proposed classification of the histopathologic features of KFD into 3 evolving histologic stages: proliferative, necrotizing, and xanthomatous. The proliferative stage consists basically of various histiocytes, plasmacytoid monocytes, and a variable number of lymphoid cells with karyorrhectic nuclear fragments and eosinophilic apoptosis debris. If cellular aggregates in a given lymph node showed any degree of coagulative necrosis, the case was classified as necrotizing. If foamy histiocytes predominated in the KFD lesions, the case was classified as xanthomatous regardless of the presence or absence of necrosis. The most common type was the necrotizing type, accounting for slightly more than half of the cases. As Kuo et al. [14] pointed out, the 3 histologic types might represent different stages of the disease or might reflect differences in cause or host reaction. Judging from the histologic changes, KFD perhaps begins as proliferative, progresses to necrotizing, and finally resolves into xanthomatous. The duration of the disease doesn’t correlate with the progression of the 3 histologic types. However; this speculation has not been confirmed because of a lack of studies with sequential biopsies.

The immunophenotype of KFD typically consists of a predominance of T-cells, with very few B cells. There is an abundance of CD8+ T-cells over CD4+. The histiocytes express histiocyte-associated antigens such as lysozyme, myeloperoxidase (MPO) and CD68. Finally, striking plasmacytoid monocytes are also positive for CD68 but not for MPO [5]. Even though the diagnosis would have been facilitated if immunohistochemistry was performed it was not carried out in this particular case.

The differentiation of KFD from SLE can sometimes be problematic because both can show similar clinical and histological features. Furthermore, KFD has been reported in association with SLE. Therefore the following features will be of help as these can be seen in SLE-associated lymphadenitis but not in KFD;

1. Hematoxylin-bodies which believed to represent degenerated nuclei that have reacted with antinuclear antibodies
2. Azzopardi phenomenon (i.e., encrustation of blood vessel walls with nuclear material).
3. Sparse cytotoxic T cells which tip the balance in favour of SLE-associated lymphadenitis, in contrast with the CD8+ lymphocyte abundance seen in lymph nodes in KFD [14].

However, these striking features might not be identified in every case of SLE-associated lymphadenitis, and the diagnosis cannot always be ruled out on histologic grounds alone [12, 13]. In our case the possible association with SLE was not considered due to negative haematological investigations and the non-contributory histopathological findings.

Nevertheless, even though there is little information in the literature about lupus-associated lymphadenitis, its immunophenotype seems to be virtually identical to that of KFD, including the CD68+/MPO+ histiocytic pattern [15]. Therefore, finally, the presence of a large number of plasma cells in a given lymph node
with features resembling those of KFD favors SLE-associated lymphadenitis over KFD [5].

The diagnosis of KFD is generally not difficult, although early lesions lacking necrosis can be misdiagnosed as malignant lymphoma, due to the presence of abundant immunoblasts [16]. Features of KFD that may help prevent its misdiagnosis as malignant lymphoma include incomplete architectural effacement with patent sinuses, presence of numerous reactive histiocytes, relatively low mitotic rates, absence of Reed-Sternberg cells (stain with CD30 or CD15 or both). However, in this case even though lymphoma was considered in the differential diagnosis, the possibility was excluded by the confirmation of the re-excision biopsy.

The recognition of KFD is necessary because one can avoid laborious investigation for infectious and lymphoproliferative diseases and to prevent the over treatment. The distinction from tuberculosis lymphadenitis is important especially in regions where tuberculosis is quite common. The epithelioid cell granuloma, multinucleated giant cells of Langhans’ type, caseous necrosis and absence of karyorrhectic debris clearly favour the diagnosis of tuberculosis [17].

Kikuchi-Fujimoto disease is typically self-limited within one to four months. A low but possible recurrence rate of three to four percent has been reported [8]. In some few patients, SLE may occur some years later. No risk of spread to other family members is felt to be associated with KFD [18]. There is no specific treatment for KFD due to its unknown aetiology however, because the disease is self-limiting, only symptomatic treatment measures are taken to relieve distressing local and systemic complaints [5]. This includes analgesics, antipyretics and anti-inflammatory medications [5]. The use of corticosteroids is reserved for severe extra nodal or generalized cases or relapsing disease, but is of uncertain efficacy.

However, our patient was started on steroids not as a treatment of KFD, but as a consequence of worsening thrombocytopenia and patient responded well and improved drastically. This improvement may be due to the natural remission of the disease or as a respond to steroids.

Further, it should also be noted that this patient’s natural history has taken longer than the reported cases in the literature. Also, the associated thrombocytopenia cannot be explained as there are very few such cases reported in the literature [10].

Patients with KFD require a systematic survey and regular follow-up for several years to rule out the development of SLE. The cervical lymphadenopathy runs a benign course and appears to resolve spontaneously one to six months after definite diagnosis [19]. However our patient is on regular follow ups for a period of six months and she is free of any recurrences or development of any autoimmune diseases up to date.

References


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