Kikuchi’s Disease: A Rare Clinical Entity of Cervical Lymphadenopathy with Review of Literature

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ABSTRACT

Background and objectives: Kikuchi disease is an uncommon, idiopathic, generally self-limited cause of lymphadenitis. The disease runs a self-limiting course usually resolving in 6 to 8 months of occurrence, with the usual clinical manifestations being cervical lymphadenopathy, with or without systemic manifestations.

Materials and methods: A retrospective study was done in three cases of Kikuchi disease reported over 2 years. All three females had cervical lymphadenopathy not responding to empirical treatment. All had excision of the lymph nodes with immunohistochemistry, which suggested the necrotizing lymphadenopathy. Other similar diagnoses, like systemic lupus erythematosus, non-Hodgkin’s lymphoma, Kawasaki, tuberculous, metastatic lymphadenopathy, were excluded.

Conclusion: The rare possibility of cervical lymphadenopathy being Kikuchi’s disease should be thought if empirical therapy fails. So, a meticulous effort by the pathologist and surgeon helps in diagnosing the self-limiting, little understood disease of Kikuchi in young patients with cervical lymphadenopathy and fever.

Keywords: Cervical lymphadenopathy, Computed tomography scan, Fine-needle aspiration cytology, Immunohistochemistry.

INTRODUCTION

Kikuchi disease, also called as Kikuchi-Fujimoto disease or histiocytic necrotizing lymphadenitis, is an uncommon, idiopathic, generally self-limited cause of lymphadenitis. The disease runs a self-limiting course usually resolving in 6 to 8 months of occurrence, with the usual clinical manifestations being cervical lymphadenopathy, with or without systemic manifestations.

Earlier, the disease was misdiagnosed as lymphoma or systemic lupus erythematosus (SLE) with minimal recurrences and complications.

MATERIALS AND METHODS

We report three cases of this disease reported in our department over the past 5 years. All the three were females around the 5th to 6th decade (mean age—51 years). They presented with cervical lymphadenopathy not subsided by two courses of antibiotics and anti-inflammatory drugs. Two had left-sided and the other right-sided cervical lymph nodes enlargement. All had posterior group enlarged, while one had the left-sided level III also enlarged (Fig. 1). Constitutional symptoms, like intermittent fever, fatigability, were present for a couple of months. Two had hysterectomy done for dysfunctional uterine bleeding and no other significant medical history. The nodes were nontender and were palpable with no increase in size. Baseline investigations were done with all the blood and urine parameters being normal with an increase in erythrocyte sedimentation rate. Fine-needle aspiration cytology (FNAC) was done in all cases, which showed a reactive picture. Chest X-ray and sputum for acid fast bacilli were negative.
Sonography of the neck suggested group of posterior triangle nodes with a mean diameter of 2 cm, while one patient also had level III node involvement (Fig. 2). Contrast-enhanced picture suggested posterior cervical lymph nodes around 2 cm and also lower jugular in all the three cases (Fig. 3). One female had inflammatory tendinitis on the left side with the lymph node excision done 5 months ago on the same side (Fig. 4). As the FNAC was inconclusive and did not subside on empirical treatment, an excision biopsy was done. Microscopy revealed an inconclusive picture of necrotizing lymphadenitis and lymphoma. Low-power sections show completely effaced lymph node architecture by necrotic change in the subcapsular region. Higher resolution pictures show collection of mononuclear cells with abundant karyotic debris (Fig. 5).

Immunohistochemistry (IHC) reported cluster of differentiation (CD)79 and CD20 highlighting the B cells, while CD3 highlighted the T cells. Plasmacytoid histiocytes were decorated by CD68 and myeloperoxidase (MPO). The patient was reanalyzed for SLE, lymphoma, and other autoimmune diseases. A rare diagnosis
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of Kikuchi disease by exclusion was done, and oral deflazacort 6 mg was given for 3 weeks daily. The enlarged lymph nodes subsided in an average of 6 weeks. The patients were followed up for 1 year with clinical examination, which did not show any recurrence.

DISCUSSION

The disease is reported in East Asia with very few incidences from Europe and North America. The disease affects young adults and is marginally more common in females. It manifests as acute onset of cervical adenopathy associated with fever and a flu-like prodrome. Cervical nodes are affected in 80%, while the posterior cervical nodes are most commonly (65–70% of cases) involved. Single level of nodes is involved in 83%, while rare involvement of multiple levels is reported. The nodes are usually painless, 2 to 3 cm in diameter, rarely may reach 6 cm, and are firm and nonfluctuant on palpation. Also, rare cases of axillary, mediastinal, celiac, inguinal, and mesenteric nodes are reported. Majority of them present with flu-like syndrome with headache, nausea, vomiting, malaise, fatigue, weight loss, arthralgias, myalgias, night sweats, rash (up to 30%), and thoracic and abdominal pain.

Self-resolving skin lesions resembling SLE are seen in 25%, manifesting as maculopapular lesions, morbilliform rash, nodules, urticaria, and malar rash. Lactase dehydrogenase (LDH) levels raised in hepatosplenomegaly are seen in few cases. Neural complications like aseptic meningitis, acute cerebellar, ataxia, and encephalitis are rare. Also seen are bone marrow, myocardium, uvea, thyroid, and parotid glands. Rare cases of asymmetric polyarthritis, enthesitis, and dactylitis of the toes are also reported. Infectious and self-limiting autoimmune etiologies have been proposed. As human leukocyte antigen (HLA) class II genes are seen in these patients, a genetic predisposition to the proposed autoimmune response is noted. Lymphadenitis results from apoptotic cell death induced by cytotoxic T lymphocytes. A viral infective etiology seen as upper respiratory tract infection has also been proposed, which includes cytomegalovirus, Epstein–Barr virus, human herpes virus, varicella-zoster virus, parainfluenza virus, parvovirus B19, and paramyxovirus. A hyperimmune reaction led by many pathogens has been suggested with no serological or molecular studies proving the same. Gallien et al and Kampitak also noted histologic appearance of lymph nodes in patients with SLE, and a mild form of the same disease had been postulated.

As already discussed, the disease is self-limiting, lymph node enlargement subsides in 6 months, while the disease may persist with a recurrence of 3%. Supari and Ananthanurthy reported a study of 24 cases which they followed up over a period of 4 years. All the 24 cases (females and males) had painless cervical lymphadenopathy, and the histopathology showed necrosis, karyorrhectic debris, and the presence of the typical cell types, namely crescentic histiocytes and plasmacytoid monocytes. All the cases resolved with 1 month of follow-up and conservative treatment. The pre-IHC era reported a series by Dorfman and Berry, where 40% of the cases were put on regimens of overkill chemotherapy. Kikuchi disease can resemble SLE with lymphadenopathy and fever, with one-third of the cases having cutaneous signs of SLE. The autoimmune antibody, like antinuclear antibodies (ANA), rheumatoid factor (RF), and lupus erythematosus (LE) are negative differentiates it from SLE. The histopathology of necrotizing lymphadenitis resembles that of SLE where neutrophils and B lymphocytes predominate in SLE, while T lymphocytes predominate in Kikuchi, with the absence or paucity of the hematoxylin bodies and plasma cells. Conditions considered as differential diagnosis include atypical mycobacterial lymphadenitis, lymphoma, metastatic carcinoma, other viral- or bacterial-caused lymphadenitis, rheumatoid arthritis lymphadenitis, and Still’s disease. Other diseases with localized lymphadenopathy include Cat-scratch disease, infectious mononucleosis, Kawasaki disease, leprosy, sarcoidosis, syphilis, toxoplasmosis, tuberculosis, and tularemia. Laboratory studies show mild granulocytopenia, which is observed in 20 to 50% of patients; leukocytosis is present in 2 to 5% of patients; atypical lymphocytes are observed in 25% of patients; C-reactive protein and ESR may be elevated, while an elevated LDH denotes hepatic involvement.

Singhania et al described histopathological characteristics of the lymph nodes where features of paracortical necrosis (pathy and confluent), crescentic nuclei, histiocytes, and other cells included lymphocytes, plasmacytoid monocytes, macrophages, and immunoblasts. Also, karyorrhexis, which means histiocytes, and macrophages
contain phagocytized debris from degenerated lymphocytes.19 Bosch et al5 defined some differential diagnosis for cervical lymphadenopathies. Systemic lupus erythematosus had elevated ANA titers with SLE features on follow-up with hematoxylin bodies, azzopardi phenomenon, sparse CD8 T cells, and abundance of plasma cells on microscopy.5 Herpes simplex-associated lymphadenopathy shows skin lesions at the neck apart from the mucus lesions.5 Microscopy shows presence of neutrophils, viral inclusions with no striking polymorphous histiocytic infiltrate, but the histiocytes take up MPO.5 Non-Hodgkin lymphoma shows no striking polymorphous histiocytic infiltrate, while most T-cell lymphomas, CD4+, and the histiocytes are MPO negative.5 Plasmacytoid T-cell leukemia seen in elderly men who have or will develop myelocytic lymphoma (MML) shows proliferation of plasmacytoid cells with no striking polymorphous histiocytic infiltrate.5 Kawasaki disease seen in children younger than 5 years with typical skin involvement with microscopy shows geographic necrosis, fibrinoid thrombosis with no striking polymorphous histiocytic infiltrate, and presence of neutrophils and absent plasmacytoid cells.5 Nodal colonization by acute myeloid leukemia shows no striking polymorphous histiocytic infiltrate with lack of CD8 T cells (CD34+; neutrophilic elastase–positive; HLA-DR+).5 Metastatic adenocarcinoma shows signet ring cells containing mucin rather than nuclear debris, while IHC shows a presence of cytokeratin with absence of histiocyte-associated antigens.5 Infectious lymphadenitis shows occasional presence of granulomas with usual presence of polymorphonuclear leukocytes with histiocytes taking up MPO.5

Computed tomography (CT) scanning and magnetic resonance imaging shows a uniform enlargement of lymph nodes with postcontrast enhancement.10 Kwon et al10 reported CT findings in 96 cases, with homogeneous lymph node enlargement in 83.3% of the patients, perinodal infiltration in 81.3%, and prominent areas of low attenuation, suggestive of focal necrosis in 16.7%. Han et al11 reported CT scan imaging patterns of 15 pediatric cases. Apart from perinodal infiltrates (10 cases 63%), which demonstrated nonenhancing necrosis clinically, 10-day median duration of fever was seen.11 Fourteen children reported cure, while a recurrence was seen in four cases.11 Sonography showed enlarged nodes either homogeneous or heterogeneous with hyperechoic rims.20 Screening chest X-ray is used to rule out tuberculosis or malignancy.14

Tong et al21 reported that the FNAC had an overall accuracy of 56.75% in diagnosing Kikuchi disease. Histopathology of excisional lymph node biopsy shows paracortical necrosis, which may be patchy or confluent and the area of necrosis varies.21 Histiocytes have crescentic nuclei that also contain phagocytized debris from degenerated lymphocytes.21 Predominant lymphocytes, plasmacytoid monocytes, macrophages, and immunoblasts are seen but with fewer neutrophils, granulomas, plasma cells.21 Kuo4 defined the histologic phases into an initial proliferative phase and a later necrotizing phase, with extensive necrosis destroying the normal architecture of the lymph node and a xanthomatous foamy cell phase with resolution of necrosis. Immunohistochemistry shows mature CD8-positive and CD4-positive T lymphocytes, with lymphocytes and histiocytes also exhibiting a high rate of apoptosis.4 Positive immunostaining results by monoclonal antibody Ki-M1P are seen in Kikuchi disease, but not in malignant lymphoma.4 Lymphoma can be ruled out by the absence of Reed–Sternberg cells, relatively low mitotic rates, presence of numerous reactive histiocytes, and incomplete architectural effacement with patent sinuses.4 The disease subsides with symptomatic treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), while potent anti-inflammatory steroids are indicated in severe extranodal or generalized disease, aseptic meningitis, cerebellar ataxia, hepatic involvement (elevated LDH level), severe lupus-like syndrome (positive ANA titers).4

Jang et al22 recommended steroids for prolonged fever and annoying symptoms lasting more than 2 weeks despite NSAID therapy, as well as for recurrent disease and for patients who desired a faster recovery. Immunosuppressants have been recommended as an adjunct to corticosteroids in severe, life-threatening disease, while the role of surgery is limited to excisional biopsy alone.22 Immunoglobulins have been tried intravenously but the role has not been proven.23 Overall, the disease is a self-limiting disease with good prognosis, with lymphadenopathy usually resolving within 1 to 6 months after the onset with a minimal recurrence of 3%.20 Kampitak2 reported three deaths with acute form of the generalized disease, while one more death was reported with a coexisting SLE, due to complications of hemophagocytic syndrome and severe infection.

CONCLUSION

The rare possibility of cervical lymphadenopathy being Kikuchi’s disease should be thought of by specialty of all platforms if empirical therapy fails. Immunohistochemistry plays a deciding role to reduce the overkill of misdiagnosis like lymphoma, tuberculosis, and SLE. So, a meticulous effort by the pathologist and surgeon helps in diagnosing the self-limiting, little understood disease of Kikuchi in young patients with cervical lymphadenopathy and fever.
REFERENCES