Kikuchi-Fujimoto Syndrome

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KIKUCHI-FUJIMOTO DISEASE COINCIDING WITH SYTEMIC LUPUS ERYTHEMATOSUS
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Objectives/Learning Points

Kikuchi-Fujimoto Disease
Kikuchi-Fujimoto Disease can be its own entity or seen with a multitude of infectious disease conditions, malignancy, and rheumatologic conditions therefore obtaining specialists to rule out disease even if the patient is clinically deteriorating is very crucial prior to starting steroids

Case:
A 15 year old Hispanic female living in Kentucky presented with 1 week of right neck adenitis. Laboratory workup utilizing gram stain and cultures of right neck mass showed gram-positive cocci in clusters suggestive of Staphylococcus aureus. The mass was removed as acute bilateral infection. She was prescribed Amoxicillin for possible strep infection. When neck pain worsened, a Neck CT showed inflammatory changes from cellulitis or phlegmon in the right supraclavicular region. Infectious disease evaluation performed with negative findings towards Histoplasmosis, Rhinosporidiosis, enterovirus, adenovirus, group A streptococcus, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, adenovirus, enterovirus, mycoplasma pneumoniae, Group A streptococcus, and influenza.

Once fungal and malignancy evaluation was complete, patient was diagnosed with Kikuchi-Fujimoto Disease with concurrent Systemic Lupus Erythematosus. She met ACR SLE positive criteria with lymphopenia, oral ulcers, non-erosive arthritis, pleuritis, and positive ANA. She was started on 1.5 mg/kg prednisone and symptoms improved for 48 hours and CRP decreased to 5.3 mg/mL. She was discharged home on prednisone and tapered over 2 months. She was then started on Plaquenil 200 mg twice a day. 5 months later CRP <0.1 mg/L and ESR 11 mm/hr with resolution of prior symptoms.

Rheumatologic labs negative with positive ANA speckled at 1:1280, anti SSA(Ro) highly positive, anti SSB(La) highly positive. Normal C3 and C4. Anti-DNA, Anti-Smith, Anticardiolipin, Anti Phospholipid Antibody, and Anti-Cardiolipin were all negative.

Kikuchi-Fujimoto Disease with negative malignancy findings. Lab workup including infectious, malignant, and autoimmune. One condition that is rarely thought of is Kikuchi-Fujimoto disease, also known as histiocytic necrotizing lymphadenitis. A pediatric hospitalist must be aware of this entity and understand the importance of identifying it. During the initial workup, a pediatric rheumatologist, infectious disease consultant, and oncologist should be involved. Empiric treatments with broad-spectrum antibiotics and adequate anti-inflammatory medications are beneficial until more diagnostic information is gathered including lymph node pathology. A differential diagnosis of cervical adenopathy is shown below.

Dermatologically performed punch biopsy on abdominal rash showing mixed perifolliculitis suggestive of reactive process such as a neutrophilic dermatitis. Right supraventricular lymph node was surgically biopsied with findings consistent with histiocytic necrotizing lymphadenitis, also known as Kikuchi-Fujimoto Disease with negative malignancy findings.

Left to Right: Circumscribed paracortical necrosis, Karyorrhectic nuclear debris

Left to Right: Right cervical lymphadenitis with overlying cellulitis, engorged, nodular rash

Acute unilateral infection
- Staphylococcus aureus
- Group A streptococcus
- Anaerobic bacteria
- Group B streptococcus
- Alpha streptococcus
- Verruca
- Gram-negative bacilli

Autoimmune conditions:
- Juvenile idiopathic arthritis
- Systemic lupus erythematosus
- Kawasaki disease
- Pemphigus vulgaris
- Kikuchi-Fujimoto disease
- Sarcoidosis
- Histiocytosis
- Castleman disease (lymphoproliferative disorder)
- Kimura disease (chronic inflammatory disorder)

Acute bilateral infection:
- Staphylococcus aureus
- Rhinovirus
- Epstein-Barr virus
- Cytomegalovirus
- Herpes simplex virus
- Adenovirus
- Enterovirus
- Mycoplasma pneumoniae
- Group A streptococcus
- Influenza

Malignant causes:
- Head and Neck Cancer
- Metastatic squamous cell Carcinoma
- Lymphoma
- Leukemia
- Neuroblastoma
- Rhabdomyosarcoma
- Thyroid cancer

Discussion

In the work up of patients with cervical lymphadenitis, a multitude of other causes need to be considered including infectious, malignant, and autoimmune. One condition that is rarely thought of is Kikuchi-Fujimoto disease; also known as histiocytic necrotizing lymphadenitis. A pediatric hospitalist must be aware of this entity and understand the importance of identifying it. During the initial workup, a pediatric rheumatologist, infectious disease consultant, and oncologist should be involved. Empiric treatments with broad-spectrum antibiotics and adequate anti-inflammatory medications are beneficial until more diagnostic information is gathered including lymph node pathology. A differential diagnosis of cervical adenopathy is shown below.

Initial labs revealed leukopenia at 4,100/uL predominantly neutrophils, normal hemoglobin, hematocrit, platelets, ESR 44 mm/hr, CRP 22.0 mg/L, Ferritin 129 ng/mL, and Albumin 2.6 g/dL. Neck CT showed inflammatory changes from cellultis or phlegmon in the right supravacular region with associated reactive lymph nodes.

Infectious disease evaluation performed with negative findings towards Histoplasmosis, Blastomycosis, ARF disease, bacterial studies, Bartonella, Toxoplasmosis, Sarcoidosis, HIV and CMV. EBV with IgG positivity and elevation to early antigen antibody. Malignancy labs negative with normal peripheral smear, normal uric acid and LDH.

Symptoms and physical findings began to progress, including painful oral aphotic ulcers, pleural chest pain, abdominal pain with splenomegaly, dry eye pain, worsening to headaches, increased swelling to 3rd DIP and new arthritis in 2nd and 4th IP.

Fever continued while on Ampicillin-Subactam and scheduled Naproxen.

References


Kikuchi-Fujimoto Disease is a histiocytic necrotizing lymphadenitis that was first diagnosed in 1972 in Japan. The disease is largely under diagnosed and not well known. A higher pediatric incidence of disease has been seen in the past 5 years mainly due to more awareness of condition. KFD is usually characterized by cervical lymphadenopathy and fever although a variety of other symptoms and physical findings occur sporadically.

Common symptoms accompanying fever were upper respiratory symptoms (cough, sore throat, and rhinorrhea), fatigue, joint pain, muscle ache, night sweats, headache, abdominal pain, diarrhea, and rash. Physical exam findings can include erythematous rash, arthritis, hepatosplenomegaly, xerostomia, and aphthous lesions with lymphadenopathy largely localized to cervical region although localized lymphadenopathy of axillary, inguinal, and abdominal region has been seen.[2]

KFD can be either a benign entity or associated with systemic conditions. Its etiology is still unknown after 45 years. Some studies propose viral infections in pathogenesis of KFD such as HIV, EBV, herpes simplex virus, EBV, CMV, and HCMV have also been proposed as triggering factors in SLE. KFD has been seen with systemic illnesses such as chronic idiopathic thrombocytopenic purpura, autoimmune thyroiditis, nephrotic syndrome, pernicious cytomegalovirus infection, and hemophagocytic lymphohistiocytosis but largely associated with autoimmune conditions such as SLE.[3]

The diagnosis of Kikuchi disease is made solely by lymph node biopsy. Pathology of KFD involves patchy areas of necrosis with karyorrhexis (breakdown of nuclear chromatin), surrounded by an inflammatory infiltrate of histocytes, lymphoma cells, and immunoblasts, and absence of granulocytes. Cell death from an apoptotic process rather than necrosis occurs. Pharmacologic therapies with interdependent karyorrhexis and crescent shaped histiocytes have been considered minimum diagnostic criterion for KFDD.[4] Immunophenotype studies show a predominance of T cells, very few B cells, and abundance of CD4+ T cells over CD4- T cells. Histopathess express histioocyte-associated antigens such as lysosome, MPO, and CD68. Lymphadenopathy associated with SLE is widespread, whereas lymphadenopathy associated with KFD is more localized, usually only affecting the cervical lymph nodes. Histologically lymph nodes evaluated in SLE and KFD are very similar and demonstrate non specific changes with the exception of necrosis. Hematokin bodies were not found in KFD.[6] In the early proliferation stage of KFD, the presence of clusters of large atypical cells and immunoblasts can be mistaken for lymphoma. In lymphoma necrosis may or may not be extensive and neutrophils and granulomata tend to be absent. Lymphoma is incorrectly diagnosed in approximately 30% of cases of KFD.[3]

Treatment for KFD is mainly supportive with NSAIDS and steroids. Some studies show that the self limited course of KFD requires no treatment while others stress the importance of steroid use. In one study involving 138 Chinese children from 1989-2006, 4 patients died that were diagnosed late who did not receive steroids immediately, and in the patients that were followed for 10 years, those whom did not receive steroids relapsed more frequently.[9] In the situations where KFD occurs with another systemic illness, the associated condition must receive treatment.