Kikuchi Disease in Connecticut

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Kikuchi disease is a self-limited disorder of unknown etiology characterized by focal painful lymphadenitis, fever, and weight loss that can be mistaken for malignancy. Diagnosis is established by node biopsy. Kikuchi disease is endemic in Asia; 10 cases have been reported in the US to date. We report 3 cases and review other US cases. *(J Pediatr 2014;164:196-200).*

In 1972, 2 Japanese groups described a new illness, termed Kikuchi disease, characterized by focal painful lymphadenitis frequently associated with fever, malaise, and weight loss.[1,2] A self-limited disorder of unknown etiology, Kikuchi disease has been reported predominantly in Asian adults, especially young women. Kikuchi disease is diagnosed based on the characteristic finding of histiocytic necrotizing lymphadenitis on lymph node biopsy. Since 1972, multiple case series have been published involving patients from Asia or travelers to Asia.[3-6]

Kikuchi disease occurs sporadically outside Asia. We have identified 10 case reports involving patients from the US.[7-16] In 2009 and 2010, we diagnosed 4 children with Kikuchi disease, 1 of whom was later diagnosed with systemic lupus erythematosus (SLE). The histology of the lymphadenitis seen in Kikuchi disease and SLE may be indistinguishable.

Methods

The Connecticut Children's Medical Center (CCMC) opened in April 1996. All lymph node biopsies performed in both the inpatient and outpatient settings are routinely sent to the Department of Pathology and Laboratory Medicine of Hartford Hospital, which is physically connected to CCMC. The 3 patients with Kikuchi disease and the 1 patient with SLE were cared for at CCMC between April 2009 and September 2010. The Hartford Hospital pathology reports from April 1996 through September 2012 were searched for additional children with Kikuchi disease or histiocytic necrotizing lymphadenitis. In addition, the computerized discharge diagnoses of all CCMC patients seen between April 1996 and September 2012 were reviewed for a diagnosis of Kikuchi disease or histiocytic necrotizing lymphadenitis.

ANA	Antinuclear antibodies
CCMC	Connecticut Children's Medical Center
CMV	Cytomegalovirus
EBV	Epstein-Barr virus
ESR	Erythrocyte sedimentation rate
LA	Anti-LA antibody
LDH	Lactate dehydrogenase
PPD	Purified protein derivative
RO	Anti-RO antibody
SLE	Systemic lupus erythematosus
SM	anti-Smith antibody
WBC	White blood cell count

Results

Between April 1996 and September 2012, approximately 580 children underwent lymph node biopsy at CCMC, 4 of whom were diagnosed with Kikuchi disease. Our search revealed no additional cases of Kikuchi disease at CCMC.

Case 1

A 17-year-old white female presented with fever and malaise in April 2009. Over the next 2 weeks, she developed a painful right anterior cervical lymph node. She was evaluated by her primary care physician, who suspected bacterial lymphadenitis and prescribed cephalexin. She subsequently developed a morbiliform rash, at which point antibiotic therapy was changed to trimethoprim/sulfamethoxazole. She then developed urticaria, prompting discontinuation of trimethoprim/sulfamethoxazole therapy. Over the next month, the lymph node enlarged slowly, and fever (38.4-40°C) and malaise persisted. She had a weight loss of ~5 kg.

The patient was seen as an outpatient at CCMC on day 58 of her illness, at which time she had a orally measured temperature of 38.0°C. Physical examination was normal with the exception of a slightly tender, 4.5 × 2 cm right anterior cervical lymph node. She had no history of travel or unusual exposures. Laboratory test results included a white blood cell count (WBC) of 2000/mm^3 with a normal differential, a platelet count of 147 000/mm^3, an erythrocyte sedimentation rate (ESR) of 51 mm/hour, and a serum lactate dehydrogenase (LDH) level of 455 U/mL (normal, 120-260 U/mL). Chest radiography was normal, and a purified protein derivative (PPD) was negative. Serologic tests were negative for cat scratch disease, Epstein-Barr virus (EBV) infection, cytomegalovirus (CMV) infection, and *Toxoplasmosis* infection. Lymph node biopsy analysis revealed pathology consistent with Kikuchi disease. No treatment was provided.

When the patient was seen on day 70 of her illness, she was asymptomatic. Her enlarged cervical node had decreased in size to 2 × 2 cm and was no longer painful. At this time,

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serum antinuclear antibodies (ANA) and antibodies to double-stranded DNA, anti-Smith antibody (SM), anti-RO antibody (RO), and anti-LA antibody (LA) also were negative. We have continued to follow the patient, and she has remained well.

Case 2

A 16-year-old white female presented in July 2009 with right-sided painful submandibular lymphadenitis with fever (38.4-39.9°C), malaise, headache, and arthralgia. She was treated for possible bacterial lymphadenitis initially with cephalexin and then with clindamycin, both without success. On day 26 of her illness, she was treated with erythromycin and subsequently developed a morbiliform rash that resolved after discontinuation of erythromycin therapy. During the first month of illness, she lost 4 kg. She was referred for hematology/oncology consultation.

Laboratory tests performed on day 33 of her illness yielded a WBC of 1800/mm^3 with a normal differential, a platelet count of 179 000/mm^2, an ESR of 50 mm/hour, and a serum LDH level of 351 U/mL. Serum hepatic enzyme levels were slightly elevated. Serum ANA and antibodies to double-stranded DNA, SM, RO, and LA were negative. Chest radiography was normal and PPD was negative. A neck computed tomography scan revealed an ~3 × 5 cm submandibular node. Serologic tests for cat scratch disease and EBV, CMV, and *Toxoplasmosis* infection were negative. On day 35 of illness, lymph node biopsy analysis revealed pathology consistent with Kikuchi disease (**Figures 1** and **2**). Over the next 3 weeks, the patient's fever and lymphadenopathy resolved without therapy, and she has remained well.

Case 3

A 13-year-old Asian male developed fever in September 2010 that reached as high as 40°C and persisted for 3 weeks. The sole associated symptoms were chills and fatigue. The patient was born and raised in Connecticut, and his parents were born in Vietnam. He had visited Vietnam once, 5 years before the onset of this illness. On day 21 of fever, he visited his primary care doctor. Physical examination revealed bilateral painful cervical lymphadenopathy. A rapid mononucleosis test was negative. His WBC was 3500/mm^3 with a normal differential, and EBV serology was negative.

The patient's fever and adenopathy continued, and he was hospitalized on day 27 of his illness. He experienced no weight loss. Chest radiography was normal, PPD was negative, and serologic tests for cat scratch disease and CMV and *Toxoplasmosis* infection were negative. Serum ANA and antibodies to double-stranded DNA, SM, RO, and LA were negative.

On the fourth day of hospitalization, a lymph node was biopsied, and the patient was discharged to be followed as an outpatient. His lowest WBC was 2800/mm^3, his lowest platelet count was 157 000/mm^3, his highest serum C-reactive protein value was 2.51 mg/dL (normal, <0.5 mg/dL), and his highest serum LDH level was 751 U/mL. Histological analysis of the biopsy specimen was consistent with Kikuchi disease. The patient's fever continued for 4 days after discharge, at which time he was treated with prednisone (2 mg/kg daily for 5 days); fever resolved within a day of initiation. Adenopathy continued for 3 more weeks and then resolved. The patient has remained well.

Case 4

A 12-year-old African-American female developed fever and right anterior cervical lymph adenopathy in June 2009. Over the next 3 weeks, fever (38.4-40.6°C) persisted, and she lost 3 kg. She was treated with 10-day course of amoxicillin/clavulanate for possible bacterial lymphadenitis, and demonstrated no response. She was hospitalized on day 21 of her illness with suspected bacterial lymphadenitis. At this time, she had a WBC of 4600/mm^3 with 14% polys and 66% bands, a platelet count of 219 000/mm^3, an ESR of 59 mm/hour, and a serum LDH level of 518 U/mL. Chest radiography was normal, and neck computed tomography revealed localized right-sided lymphadenopathy, 4 × 4 cm, with no drainable fluid. She was treated with intravenous vancomycin and ceftriaxone. Serologic tests for cat scratch disease, EBV, CMV, and *Toxoplasmosis* infection were negative, and PPD was negative.

On day 4 of hospitalizationm she demonstrated no response to the antibiotic therapy. The lymph node was biopsied, and analysis revealed pathology consistent with Kikuchi disease. Serum ANA and antibodies to double-stranded DNA, SM, RO, and LA were negative.

Over the next 3 weeks, the patient's fever and lymphadenitis resolved gradually without treatment. She remained well until October 2009, when she developed pandemic influenza A (H1N1). In November 2009, she was hospitalized with presumed postinfluenza demyelination syndrome. Magnetic resonance imaging showed areas of probable demyelination in the temporal lobe, frontal lobe, and cerebellar peduncle. She was treated with corticosteroids, and recovered over the subsequent 12 weeks. Repeat testing for serum antibodies associated with SLE were negative. She was referred to a neurologist/immunologist in Boston, who also detected no antibodies for SLE and deemed her initial lymph node biopsy analysis consistent with Kikuchi disease.

Over the next 6 months, the patient developed positive serum ANA and antibody to double-stranded DNA. She also experienced episodic oral ulcerations. The patient is currently being treated for SLE. In retrospect, the patient's episode of Kikuchi disease actually could have been SLE-associated lymphadenitis.

Pathological Findings

Histology. The pathological findings were similar in all 4 cases, and cultures for bacteria and mycobacteria were negative. In case 2 (**Figure 1**), histological sections demonstrated preserved but distorted lymph node architecture with a mixed inflammatory cell infiltrate that had a varied appearance, including areas of cellular proliferation and areas of necrosis. Proliferative areas in the lymph nodes (**Figure 1**, A and B) contained numerous histiocytes, including histiocytes with twisted or crescent-shaped nuclei (**Figure 1**, B), admixed with small and large lymphocytes and some immunoblasts. Apoptotic cells were interspersed