

Kikuchi's Disease in Asian Children

Hsin-Ching Lin, MD, FARS*; Chih-Ying Su, MD*; and Shun-Chen Huang, MD†

ABSTRACT. *Objective.* Kikuchi's disease (KD), or histiocytic necrotizing lymphadenitis, is a unique form of self-limiting lymphadenitis and typically affects the head and neck regions. It usually occurs in young adults and has a female predilection. The aim of this study was to review the authors' institutional experience with KD in children over a 16-year period.

Methods. Between January 1986 and May 2002, a total of 23 patients who were younger than 16 years underwent cervical lymph node biopsies and received a diagnosis of KD. Clinical features, laboratory values, pathologic parameters, specific characteristics of our pediatric patients, and long-term follow-up results are discussed. The follow-up period averaged 8 years.

Results. There were 8 girls and 15 boys with a mean age of 12.8. All 23 patients had affected cervical lymph nodes located in the posterior cervical triangle, and 2 cases additionally had affected nodes in the anterior triangle. Cervical lymph nodes were affected unilaterally in 82.6% (19) and bilaterally in 17.4% (4) of these patients. The dimensions of the affected lymph nodes were commonly in the range of 0.5 to 3 cm (52.2%; 12 of 23) and 3 to 6 cm (39.1%; 9 of 23). In 2 (8.7%) patients, the size of the enlarged lymph nodes reached >6 cm. Leukopenia was observed in 5 (21.7%) patients, and fever was observed in 7 (30.4%) patients. One child with KD developed systemic lupus erythematosus 5 years later. The cervical lymphadenopathy usually resolved itself without any medical treatment within 6 months after definite diagnosis was made. Neither recurrence nor persisting KD has since been noted.

Conclusion. KD, although rare, should be part of the differential diagnosis for posterior cervical lymphadenopathy in children, especially in patients of Asian descent. In our pediatric series, KD demonstrated a male predominance, which is in contrast to previously reported adult series demonstrating a female predominance. The children with KD require a systemic survey and regular follow-up for several years to rule out the development of systemic lupus erythematosus. *Pediatrics* 2005;115:e92–e96. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-0924; *Kikuchi's disease, cervical lymphadenopathy, neck mass, children.*

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ABBREVIATIONS. KD, Kikuchi's disease; SLE, systemic lupus erythematosus; FUO, fever of unknown origin; CT, computed tomography; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

Although neck masses are frequently encountered in the pediatric population, physicians who care for a child with a cervical mass are often faced with a diagnostic challenge. In actual practice, in child cases, it may be difficult to obtain a clear patient history and cooperative physical examination, and there are few straightforward processes for evaluation of these children. Thus, a thorough knowledge of the clinical entities that may cause neck masses in the pediatric population and the comprehensive elucidation of clinical characteristics that may help in establishing a correct diagnosis are essential.

Kikuchi's disease (KD), also called histiocytic necrotizing lymphadenitis or Kikuchi-Fujimoto disease, was first described in 1972 in Japanese literature independently by Kikuchi¹ and Fujimoto et al² as a benign, self-limiting disorder of unknown origin. The first report in English was published in 1977, and Gleeson et al³ reported the first case in the otolaryngologic literature in 1985. To date, most reports on KD entity have appeared in the pathology literature covering certain important pathologic diagnostic characteristics of KD but have received little attention in pediatric publications.

KD has been reported to have a predilection for young women under the age of 30 years in an ~3 to 4:1 ratio and is seldom reported in children.^{4–6} It manifests clinically with lymphadenopathy, typically in the head and neck regions. Some patients may also show low-grade fever; fatigue; malaise; and occasionally headache, nausea, vomiting, diarrhea, and weight loss. No diagnostic laboratory tests are available for KD. The definite diagnosis of KD can be made reliably only via histopathologic study from an open biopsy of the affected lymph nodes. The intermingling of distinctive crescentic histiocytes, karyorrhectic debris, and plasmacytoid monocytes in the form of nodules and the paucity of neutrophils are consistent findings that should permit a confident histopathologic diagnosis of KD.⁷ Although this disease has its distinctive clinical and pathologic features, it occasionally has been attributed wrongly to other causes of cervical lymphadenopathy, such as malignant lymphoma, systemic lupus erythematosus (SLE), tuberculosis, or other serious diseases. This pathologic misinterpretation has led to some patients' undergoing extensive diagnostic workups and

even chemotherapy.^{4,8,9} To the best of our knowledge, there has been a lack of comprehensive study about KD in children, and only a few case reports on pediatric KD have ever been described in the literature.

METHODS

This study was conducted at the Chang Gung Children's Hospital, Chang Gung Memorial Hospital, Kaohsiung Medical Center (Kaohsiung, Taiwan), a large tertiary care center with 2500 beds. The medical records of all children who were younger than 16 years, underwent cervical lymph node biopsies, and received a diagnosis of KD were reviewed retrospectively from January 1986 to May 2002. The pathologic slides of all patients were reviewed, and the diagnosis of KD was confirmed by a senior pathologist. Information on the age, gender, clinical presentation, symptoms and signs, duration of mass, season, site and size of mass, laboratory studies, additional imaging modalities, treatment, concomitant medical problems, and results of long-term follow-up were collected and analyzed. The follow-up data were obtained by direct survey of the pediatric patients in an outpatient facility, chart review, and telephone contact. Ethics approval was obtained from the Institutional Review Board of the Chang Gung Memorial Hospital to review patient records.

RESULTS

Twenty-three pediatric patients with KD of the head and neck regions were identified during the 16-year period (Table 1). Eight (34.8%) patients were girls, 15 (65.2%) patients were boys, and the female-to-male ratio was 1:1.9. Their age ranged from 6 to 16

TABLE 1. Summary of KD in 23 Children in Chang Gung Children's Hospital, Chang Gung Memorial Hospital, Kaohsiung

Result	No. of Patients (%)
Gender	
Male	15 (65.2)
Female	8 (34.8)
Age, y	
6-10	2 (8.7)
10-16	21 (91.3)
Season of onset	
Spring	4 (17.4)
Summer	7 (30.4)
Autumn	4 (17.4)
Winter	8 (34.8)
Site of lymphadenopathy	
Posterior cervical only	21 (91.3)
Anterior cervical only	0 (0)
Combined anterior and posterior cervical	2 (8.7)
Laterality of lymphadenopathy	
Bilateral neck	4 (17.4)
Right neck	12 (52.2)
Left neck	7 (30.4)
Painful lymphadenopathy	5 (21.7)
No. of palpable nodes	
Single	6 (26.1)
Multiple	17 (73.9)
Size of lymph node, cm in diameter	
<3	12 (52.2)
3-6	9 (39.1)
>6	2 (8.7)
Fever >37.5°C	7 (30.4)
White blood cell count	
Leukopenia	5 (21.7)
Within normal level	17 (73.9)
Leukocytosis	1 (4.4)
Associated with SLE	1 (4.4)
Resolved time, mo	
<6	18 (78.2)
6-12	4 (17.4)
>12	1 (4.4)

years (mean: 12.8 years), with 2 children younger than 10 years. A total of 189 cervical lymph biopsies were performed on children at our hospital during the study period, so KD accounted for 12.2% (23 of 189) of these biopsies. The incidence of cases did not show any particular trend per year during the study period. There was a slight seasonal variation, with 17.4% (4 patients) of the cases presenting in the spring, 30.4% (7 patients) presenting in the summer, 17.4% (4 patients) presenting in the autumn, and 34.8% (8 patients) presenting in the winter. Two patients were referred from local primary care doctors with a fever of unknown origin (FUO). Two children had a history of tuberculosis and had received a complete antituberculosis therapy 3 and 5 years previously. All 23 cases had a smooth birth history and had completed the Taiwanese scheduled vaccinations. No patient had any history of travel to foreign countries within 6 months before their doctor visit.

The duration of lymphadenopathy before diagnosis ranged from 3 days to 6 months. In all 23 cases, the posterior cervical triangle lymph nodes were involved, and 2 cases also demonstrated anterior triangle involvement. Four (17.4%) patients had bilateral involvement of the neck, 12 (52.2%) patients presented with nodal involvement of the right neck only, and 7 (30.4%) patients presented with nodal involvement of the left neck only. Single nodes were affected in 6 (26.1%) of 23 cases and multiple nodes in 17 (73.9%) cases. The rate of patients who presented with pain, induration, or nodal adherence to surrounding tissue is described in Table 1. The greatest dimension of the enlarged cervical nodes ranged from 0.5 to 8 cm, <3 cm in 12 (52.2%) patients, and 9 (39.1%) patients had 3- to 6-cm lesions. Two (8.7%) patients had a mass >6 cm in its maximal diameter.

Chest radiographs were normal in all 23 patients who had this test done. Elevated body temperature (>37.5°C) was noted in 7 (30.4%) patients. Leukopenia with a white blood cell count fewer than $3.9 \times 10^9/L$ in boys and $3.5 \times 10^9/L$ in girls was noted in 5 (21.7%) of the 23 patients, whereas leukocytosis $>10.6 \times 10^9/L$ was observed in only 1 (4.3%) patient. Among the patients who had leukopenia, 1 child was also found with atypical lymphocytes in the peripheral blood and received a bone marrow study under the presumptive diagnosis of lymphoma. Because of no remarkable findings, the patient then underwent excision biopsy of the enlarged cervical lymph nodes, which resulted in the definite diagnosis of KD.

Patients were followed for 2 to 16.8 years (mean: 8 years) after a biopsy. The remaining affected lymphadenopathy generally seemed to resolve without special treatment within 6 months (78.3%; 18 of 23), 6 to 12 months (17.4%; 4 of 23), or >1 year (4.3%; 1 of 23). One 16-year-old boy developed SLE with lupus nephritis 5 years after the diagnosis of KD. Neither recurrence of KD nor other consequences have been noted until now, other than this single SLE case.

DISCUSSION

Approximately 55% of children in all age groups have palpable lymph nodes that are not associated

with infection or systemic illness.¹⁰ Although the chances of a malignant lesion presenting as a head and neck mass in children are much lower than in adults, enlarged masses in children often lead to anxiety in both parents and physicians and may result in inappropriate management. Therefore, histopathologic diagnosis remains the gold standard in distinguishing the cause of pediatric neck masses and ruling out malignant disease.¹⁰⁻¹²

KD, a unique form of self-limiting lymphadenitis with unknown cause, usually occurs in young adults and has a female predilection, in an ~3 to 4:1 ratio.^{5-7,13} In the literature, the demographic predisposition for KD showed that most patients with the disease have been Asian, and many of the cases reported in Europe and the United States involved patients of Asian descent.^{5,7,9,13,14} Nikanne in his 1997 study mentioned that there had been only 3 reported KD cases in Scandinavian countries, only 1 of which was non-Asian.¹³ Although our previous study¹⁴ and other literature^{7,15} addressing the female predominance in the Asian population was not as striking as in the studies performed in Western countries, KD still preferentially affected young female individuals. However, the gender incidence of KD in our pediatric series has a completely different predominance compared with the adult population and shows a preference for boys with a 1.9:1 male to female ratio. The difference in gender predominance from other series may be attributable to this being a single report with small numbers and therefore not being representative of true incidence. In previous studies, a viral or postviral hyperimmune reaction has been proposed to explain the cause of KD,¹³ but this does not include the different immune responses of boys and girls or of children and adults. Additional investigation is needed. KD mainly affects young women in their third and fourth decades, and patients younger than 16 years are seldom affected and patients younger than 10 years are more rarely described.^{4,7,15-17} The youngest child in this study was 6 years old, and 2 (8.7%) patients were younger than 10 years. Some authors have suggested that there is a seasonal variation in the disease incidence; more pediatric KD patients were treated in our hospital in the summer (30.4%; 7 of 23) and winter (34.8%; 8 of 23). We found a slight seasonal variation, with most of our cases occurring in the spring and in the winter, which may be attributable to this being a single report with small numbers or to increasing pediatric outpatient department visiting cases, during spring and winter vacation.

Clinically, KD manifests with lymphadenopathy, typically in the head and neck area. Some KD case reports documented KD patients who initially were presented as FUO.^{18,19} In the current series, 2 (8.7%) children who were referred from local primary care presented with FUO without initial evidence of lymphadenopathy. The enlarged nodes developed 1 and 3 days after admission. Therefore, in children with FUO, KD should be part of the differential diagnosis. The site of KD cervical lymphadenopathy has a tendency to be located in the posterior triangle, ranging from 48% to 77% of cases in the litera-

ture.^{9,14,15,20} However, the predilection is more obvious in this pediatric series, with 100% of the patients having posterior cervical triangle lesions. Five (21.7%) patients complained of pain over the affected nodal area. Unilateral involvement (82.6%; 19 of 23) and presentation with multiple nodes (73.9%; 17 of 23) dominate in this pediatric series. In this series, the size of the masses were <6 cm (91.3%; 21 of 23), but 1 child still had a mass that reached up to 8 cm of nodal diameter. The laterality, numbers, and size of enlarged nodes in this pediatric KD series reveal the same affected status as the previous literature documenting the general population.^{5-7,9,14-16}

No radiographic finding specific to KD has been established to make a concrete diagnosis. Nonetheless, a chest radiograph should be obtained during the workup of cervical lymphadenopathy to look for evidence of tuberculosis or malignancy.²¹ All chest radiographs of our KD children were nonsignificant. Computed tomography (CT) scan of the neck may be helpful before biopsy. On CT, KD lymphadenitis might exhibit uniformly enlarged cervical lymph nodes and show enhancement on postcontrast images. The findings of CT scan on KD can also be similar to lupus lymphadenitis and malignant lymphoma.²¹ The patients should lie down immobile for 5 to 8 minutes to complete the CT examination; it might be difficult in the smaller and more uncooperative child and make it necessary to administer some sedatives, so we did not routinely arrange CT study for our pediatric patients with neck masses, except in complicated or malignant cases. Laboratory tests are helpful in ruling out the causes of cervical lymphadenopathy, but no specific tests are available for detecting KD. KD patients may have mild leukopenia, elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), or, more rarely, leukocytosis.^{6,7,14-17} Leukopenia has been frequently mentioned in 16.6% to 58.3% of KD patients^{7,9,14-17} and observed in 21.7% (5) of our 23 pediatric KD patients. ESR and CRP were not routinely checked in our cases, but the values of the tests were generally increased. Elevated ESR and CRP were noted in 72.7% (8 of 11) and 72.2% (13 of 18) of the tested patients, respectively.

Turner et al⁹ presented the first article regarding KD in 1983 in the United States. Up to 40% of their cases initially had been mistaken for large cell lymphoma, Hodgkin's disease, and other cancers and led to extensive diagnostic workups, including bone marrow or liver biopsies, and radiographic studies. Dorfman and Berry¹⁶ also reported that ~30% of cases of KD were originally misinterpreted as malignant lymphoma; thus, the ability to differentiate is crucial. The morphologic hallmarks of KD can be summarized as follows^{6,4,20}: (1) patchy, circumscribed areas of eosinophilic necrosis in the paracortex and/or cortex; (2) significant karyorrhexis with fragments of nuclear debris, nuclear dust, distributed in an irregular pattern throughout the area of necrosis; (3) absence of granulocytes in the areas of necrosis; (4) paucity of plasma cells in the involved nodal tissue; (5) clusters of plasmacytoid T cells or plasmacytoid monocytes; and (6) presence of transformed

lymphocytes (immunoblasts), predominantly of T-cell origin. The differential diagnosis of KD includes malignant lymphoma, SLE, cat-scratch disease, toxoplasmosis, acquired immunodeficiency syndrome, *Yersinia* lymphadenitis, Kawasaki's disease, and infectious mononucleosis.^{4,16} Lerosy et al⁴ particularly emphasized the difference among KD, malignant lymphoma, and Still's disease, especially in children. The CT features of KD may also mimic those of malignant lymphoma, owing to their homogeneously enhancing character without nodal necrosis.²² Definite diagnosis can be established only by open biopsy under the strict collaboration between an otolaryngologist and a pathologist.

Previous literature on KD frequently addressed the association between KD and SLE, and the reported rate was 1.3% to 7% in the general population.^{9,14,16,23–26} Clinical clues to support the relation between KD and SLE are that both diseases frequently affect young women and can precede, follow, or coincide with each other.^{6,7,9,14–16,23,24} The pathologic resemblances may also support a link between KD and SLE. Lupus lymphadenitis may contain foci of necrosis and be characterized by histiocytic and immunoblastic infiltrates; sometimes it was indistinguishable from KD lymphadenitis. However, a prominent plasma cell component and the presence of hematoxylin bodies will confirm a diagnosis of SLE. Imamura et al²⁵ further found tubuloreticular structures, an ultrastructural feature present in glomerular endothelium and peripheral lymphocytes of SLE, in lymph nodes from KD cases. Eisner et al²⁶ mentioned that perhaps KD and SLE share a common inciting event, such as exposure to an environmental or infectious agent, that can produce either disorder. Alternatively, KD may be an autoimmune-mediated necrotizing lymphadenitis that can remain self-limiting or develop into SLE. Both KD and SLE share some common clinical, pathologic, and ultrastructural features, and this may support a strong association between KD and SLE. As the data and awareness of the association between the 2 diseases grow, the optimal frequency and length of follow-up can be determined. One (4.4%) of our KD children developed SLE with lupus nephritis 5 years after the diagnosis of KD. In the literature, other reported KD-associated disorders have been meningitis,^{27,28} ruptured silicone breast implants,²⁹ breast cancer,³⁰ and buccal cancer.¹⁴

After the diagnosis of KD, most authors advise no special treatment. In cases in which KD co-occurs with SLE or in complicated cases with increased lactate dehydrogenase and serum antinuclear antibody titers, the use of corticosteroids or immunosuppressants has been recommended to prevent a fatal outcome.^{13,23,31–33} O'Neill et al³⁴ reported the only child fatality associated with pathologic features of KD, but the final cause of death in that case remains unproved even after postmortem examination. KD lymphadenopathy usually disappears completely without special treatment in a matter of several weeks to 6 months. In most (78.3%; 18 of 23) of our pediatric cases, the affected enlarged nodes resolved spontaneously within 6 months after biopsy. Al-

though recurrent KD has been reported, ranging from 1.3% to 4%, the disease still shows excellent prognosis without malignant transformation after having repeated biopsy-proven KD.^{6,7,15} In the current study, all children recovered with complete resolution of the affected lymph nodes, and no recurrence has since been noted during the follow-up period.

CONCLUSION

The results of this study demonstrate that KD in children has a completely different gender predominance compared with the adult population, showing a preference for boys. Pediatric KD is a self-limiting disorder that does not require specific management. KD, although rare, should be part of the differential diagnosis for posterior cervical lymphadenopathy in children, especially in patients of Asian descent. The children with KD require a systematic survey and regular follow-up for several years to rule out the development of SLE.

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