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Clinical manifestations of Kikuchi's disease in southern Taiwan

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Histiocytic necrotizing lymphadenitis, or Kikuchi's disease (KD), is a self-limiting cervical lymphadenitis of unknown origin. The diagnosis of KD is problematic due to the lack of specific laboratory tests. This study reviewed the clinical characteristics of 58 patients with KD. Clinical manifestations were of considerable diversity. The mean age of patients was 24.88 ± 7.44 years and there was a female predominance (1.76:1). The most frequent clinical findings were enlarged tender lymph nodes (50%), fever (43%), sore throat (21%), non-productive cough (12%), headache (10%), chills (9%) and rhinorrhea (9%). The most common initial laboratory abnormalities were leukopenia (29%), elevated erythrocyte sedimentation rate (14%), liver function impairment (14%), elevated C-reactive protein level (12%), and anemia (10%). Most patients had unilateral lymph node involvement (79%), which was usually located in the posterior triangle of the cervical lymph nodes (90%). Most patients had no comorbid disease (93%). No recurrence occurred. KD should be included in the differential diagnosis of fever with cervical lymphadenopathy.

Key words: Apoptosis, differential diagnosis, histiocytic necrotizing lymphadenitis, Kikuchi's disease, signs and symptoms

Kikuchi's disease (KD), also called histiocytic necrotizing lymphadenitis (HNL), was first described by both Kikuchi and Fujimoto et al in 1972 [1,2]. KD is characterized by localized cervical lymphadenitis, low-grade fever, malaise, fatigue, diarrhea and sometimes the condition is accompanied by sore throat, headache, rhinorrhea and body weight loss. There are no specific laboratory tests available for the diagnosis of KD, but leukopenia and elevated erythrocyte sedimentation rate (ESR) are characteristic findings. A definitive diagnosis can only be made histopathologically on lymph node biopsy tissue [3,4].

The true incidence of KD is unknown [5-8]. The clinical course is usually benign, with spontaneous remission within 1-2 months [6]. Recurrence of KD has been reported to occur in about 3% of patients, but severe complications and mortality are exceedingly rare [9-14]. The lack of bacterial etiology precludes the use of antibiotics in treatment. Acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), and prednisolone are typically used for symptomatic control. This retrospective study evaluated the initial clinical characteristics of KD in patients from southern Taiwan.

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Materials and Methods

Fifty eight consecutive patients with KD [1,2] treated at Kaohsiung Veterans General Hospital, from January 1994 through January 2004, were included in the study. Clinical basic data and laboratory results were obtained from medical records when available. All patients included in the study had the characteristic lymph node biopsy findings of abundant histiocytes that phagocytose apoptotic cells and nuclear debris (Fig. 1 and Fig. 2). All diagnoses of KD were confirmed by a staff pathologist. Statistical analyses was done using Statistical Package for the Social Sciences (SPSS) 10.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Table 1 summarizes the demographic and clinical features of the 58 KD patients. There were 21 men and 37 women, with a male:female ratio of 1:1.76. Their

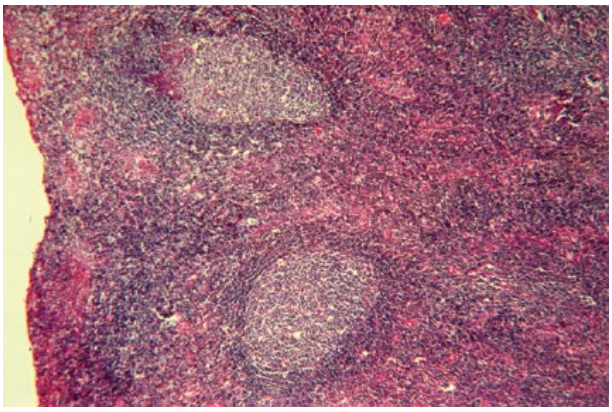

Fig. 1. Cervical lymph node biopsy shows patchy replacement of normal lymph node architecture by irregular pale cellular areas, with prominent individuals cell necrosis; low magnification (hematoxylin and eosin stain, × 40).

mean age was 24.88 ± 7.44 years (range, 9-54 years). Most patients were women under 30 years of age (70.6%), while 13 (22%) patients were younger than 18 years of age. Right, left, and bilateral cervical lymph node enlargement was found in 19 (32.7%) 27 (46.5%), and 12 (21%) patients, respectively. Lymphadenopathy in the posterior triangle of neck was found in 52 (90%) of the 58 patients. In 6 patients (10%), the lymphadenopathy was located in the anterior triangle of the neck (Table 2). The diameter of the enlarged cervical lymph nodes ranged from 0.5-9 cm. The diameter of the involved lymph nodes was smaller than 2 cm in most patients (75%), with the involved lymph nodes usually being multiple and discrete, with a rubbery or firm consistency. Occasionally, patients presented with generalized lymphadenopathy. Axillary lymph nodes were involved in 3 patients, bilateral axillary lymph nodes in a single patient, and unilateral axillary

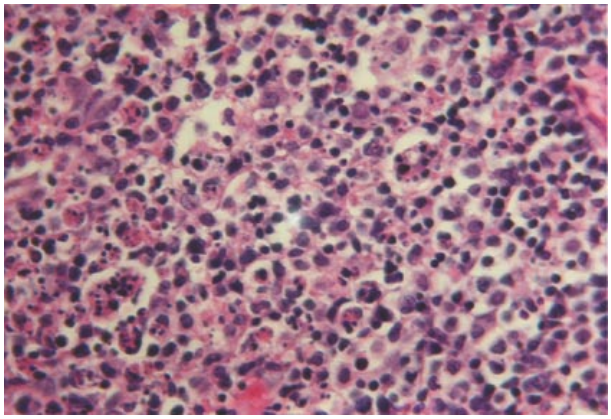

Fig. 2. High magnification shows the karyorrhexis and numerous histiocytes containing phagocytosed nuclear debris; high magnification (hematoxylin and eosin stain, × 400).

Table 1. Demographic, clinical and laboratory findings of 58 patients with Kikuchi's disease in southern Taiwan treated from January 1994 through January 2004

Demographic characteristics	No. of patients (%)
Gender	
Female	37 (64)
Male	21 (36)
Age (years)	
<18	13 (22)
>18	45 (78)
Mean ± SD (range)	24.88 ± 7.44 (9-54)
Clinical symptoms/signs	
Tender lymph node	29 (50)
Fever	25 (43)
Sore throat	12 (21)
Non-productive cough	7 (12)
Headache	6 (10)
Chills	5 (9)
Rhinorrhea	5 (9)
General malaise	3 (5)
Poor appetite	2 (3)
Body weight loss	2 (3)
Diarrhea	2 (3)
Skin rash	2 (3)
Polyarthralgia	2 (3)
Splenomegaly	2 (3)
Night sweating	1 (2)
Odynophagia	1 (2)
Foreign body sensation	1 (2)
Local heat	1 (2)
Hoarseness	1 (2)
Limitation of range of motion of the neck	1 (2)
Laboratory findings	
Leukopenia (<4000/mm^3)	17 (29)
Elevated ESR (>20 mm/h)	8 (14)
Impaired liver function (GPT >40 U/L)	8 (14)
Elevated CRP (>0.6 mg/dL)	7 (12)
Anemia (M <13.0 g/dL, F <12.0 g/dL)	6 (10)
Elevated LDH (95-205 U/L)	4 (7)
Thrombocytopenia (150-450 × 10^3/μL)	4 (7)
Atypical lymphocytes	2 (3)
Leukocytosis (>12,000/mm^3)	2 (3)

Abbreviations: SD = standard deviation; ESR = erythrocyte sedimentation rate; GPT = alanine aminotransferase; CRP = C-reactive protein; M = male; F = female; LDH = lactate dehydrogenase

in 2 patients (Table 2). Twenty nine patients (50%) presented with tenderness, while the remaining patients did not have pain or tenderness.

The duration between the detection of a cervical mass and visit for clinical help was 1-6 days in 3 patients (5.1%), up to 4 weeks in 26 patients (44.8%), and 1 month or longer in 23 patients (39.7%). Six patients

Table 2. Analysis of characteristics of involved lymph node in Kikuchi's disease (KD)

Location of involved lymph nodes	No. of patients with KD (%)
Laterality of lymphadenopathy	
Unilateral cervical	46 (79)
Right cervical	19 (32.7)
Left cervical	27 (46.5)
Bilateral cervical	12 (21)
Axillary[a]	3 (6)
Location of neck	
Posterior triangle	52 (90)
Anterior triangle	6 (10)
Size of involved lymph nodes	
<2 cm	36 (75)
>2 cm	12 (25)

[a]Three patients presented with simultaneous involvement of cervical and axillary lymph nodes, 2 with unilateral axillary lymph node involvement, and 1 with bilateral axillary lymph node involvement.

(10.3%) could not clearly delineate the time of onset of lymphadenopathy. Most patients initially sought help through ear, nose and throat clinics (45%), general surgery clinics (22%), or infection clinics (12%). For unknown reasons, the incidence of KD tended to increase during some months of the year, especially in July (Fig. 3 and Fig. 4).

Tender lymph nodes (50%), fever (43%) and sore throat (21%) were the most common presenting symptoms among patients in this study. Some patients presented with an upper respiratory prodrome including chills, sore throat, non-productive cough, headache, and rhinorrhea. Fever (>37.5°C) was observed in 25 patients (43%), with an average duration of 6.2 days (range, 2-11 days). The medication used included acetaminophen (n = 13), prednisolone (n = 4), and NSAIDs (n = 4). A small number of patients presented with general malaise, watery diarrhea, poor appetite, night sweating, odynophagia, local heat, foreign body sensation, body weight loss

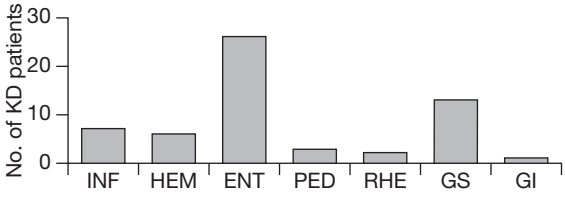

Fig. 3. The hospital departments where initial evaluation of 58 patients with Kikuchi's disease (KD) enrolled in the study was performed. INF = infection; HEM = hematology; ENT = ear-nose-throat; PED = pediatrics; RHE = rehabilitation; GS = general surgery; GI = gastrointestinal.

and limited range of neck motion. Skin rash and polyarthralgia were found in only 2 patients, and splenomegaly was found on sonography in another 2 patients.

Thirty nine patients (67%) presented with normal leukocytes counts, while leukopenia (white blood cell count, <4000/mm^3) was found in 17 patients (29%). White blood cell counts were never less than 1000/mm^3. Only 2 patients (3%) presented with leukocytosis. Eight patients had an elevated ESR, 7 patients had an elevated C-reactive protein, 7 patients had impaired liver function, 6 patients had anemia, and 2 patients had thrombocytopenia. Only 4 patients presented with an elevated lactate dehydrogenase titer and 2 patients had atypical lymphocytes on peripheral blood smear.

Major underlying diseases were rare, since 70.6% of the patients were younger than 30 years old. Only 4 older patients (7%) presented with major underlying diseases, which included pulmonary tuberculosis, epiglottic squamous cell carcinoma, urinary tract stone, and rheumatoid arthritis. One patient had a family history of systemic lupus erythematosus (SLE).

The prognosis of KD was generally favorable. Almost all patients (93%) were alive and well with complete resolution of the remaining lymph nodes at follow-up durations from 6 months to 6 years (mean, 3.8 years). Four patients presented with a smaller lymph node in the original location 1-3 months later. There was no recurrence of KD in this study.

Discussion

KD is a form of necrotizing lymphadenitis with characteristic histological features, which was first described as a distinctive type of lymphadenitis by Kikuchi and Fujimoto in 1972 [1,2]. It is a benign self-limiting lymphadenopathy of the neck. In 1989, the first case of fatal KD was reported by Chan et al [11]. In recent years, KD has become increasingly more recognized [9,10].

KD is usually a benign, self-limiting lymphadenopathy, with a histological picture of HNL. No definite etiologic factor has been identified, although a viral etiology has been suspected to include Epstein-Barr virus, human herpes virus 6, rubella virus, paramyxovirus and parainfluenza virus [15-17]. Other suspected but unconfirmed agents include parasites (*Toxoplasma*) and bacteria (*Yersinia enterocolitica*) [3]. A viral infection may trigger KD, with the subsequent development of an immune reaction of the lymph nodes. KD can be considered as a clinical disorder involving an inadequate

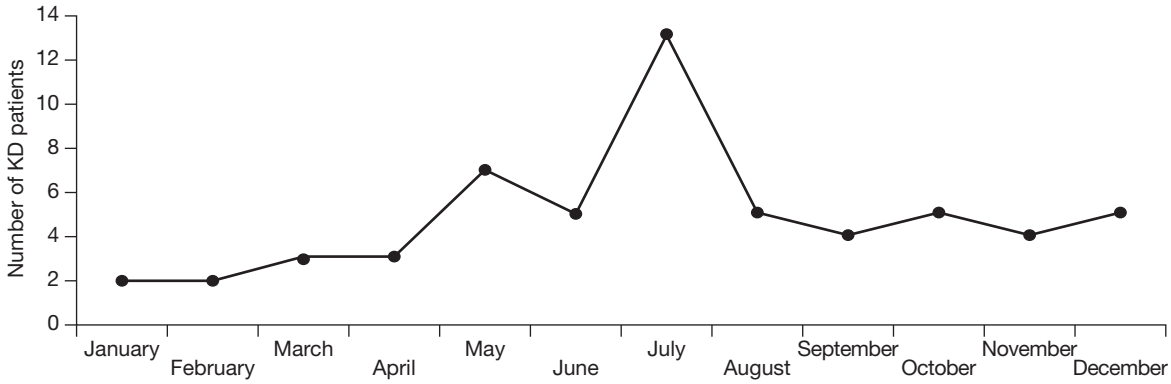

Fig. 4. Monthly distribution of visits for medical help in 58 patients with Kikuchi's disease (KD) treated from 1994 to 2004.

immunological reaction. Cytokines that are suspected of being involved include interferon-γ and interleukin-6 [18]. Tubuloreticular inclusions have been found in lymphocytes of involved lymph nodes on electron microscopy [3].

Programmed cell death is a fundamental biological process whose participation in the pathogenesis of KD is just now being appreciated [19-22]. KD is associated with an excess of apoptotic bodies of lymphocytes. One mechanism for host cells to control the spread of viral infection is to undergo apoptosis, thereby limiting viral infection. Defects in apoptosis have been shown to play a role in the pathogenesis of KD [20]. Activation of CD8-positive cells by viral infection may induce apoptosis of CD4-positive cells. The apoptotic cells are engulfed by macrophages, resulting in the presentation of typical necrotizing lymphadenitis of KD. Several investigators have suggested that KD is due to dysregulation of macrophage-mediated T-cell apoptosis [23,24].

The etiology of KD remains unclear. It has been proposed that KD is a self-limited SLE-like autoimmune condition induced by virus-infected transformed lymphocytes [25]. There is probably no one single cause for KD, which is characterized by florid lymphocytic and histiocytic proliferation. The disease is possibly a hyperimmune action to different etiological agents, be they microbial, chemical, physical or neoplastic. Chiu et al used polymerase chain reaction and in situ hybridization to document the expression of Epstein-Barr virus (EBV)-encoded RNA and Fas ligand [15]. Fas ligand expression is a mechanism that can be associated with apoptosis in HNL. Fas is a membrane protein with a molecular weight of 45,000 that induces cells to initiate apoptosis. The apoptosis in KD is caused by the Fas-Fas ligand system [19]. But positive serologic data may result from recent EBV exposure, and such data may not indicate the presence of virus at the time of lymph node biopsy. Chiu et al [15] reported EBV as a possible causative agent in KD, but this observation remains unconfirmed.

KD is often overlooked in clinical practice [26]. Tender lymph nodes, fever, chills, sore throat, headache, rhinorrhea, and polyarthralgia suggest the presence of an infectious or autoimmune disease in young women. The predilection of this entity for cervical lymph nodes is indeed striking; it affects this site in nearly 80% of those who are afflicted. The next most common sites of lymph node involvement are the axillary (14%) and then supraclavicular (12%) nodal chains [6]. In this study, lymph node involvement was in the posterior triangle of the neck in 52 cases (90%). Only 6 cases (10%) had lymph node involvement in the anterior triangle of the neck, which is consistent with a previous study [6].

The true incidence of KD is unknown. An increased incidence in females has been reported, with a female-to-male ratio between 1.1:1 to 4:1 [5,6], while the female-to-male ratio in this study was relatively low at only 1.76:1. A relatively low female-to-male ratio in an Asian series was reported by Kuo in 1995 [4]. In a previous pathologic study of lymph node disease in Taiwan, KD accounted for 5.7% of lymph node biopsy specimens [4]. About 30% of cases of KD have extra-nodal involvement, including the skin, brain, and bone marrow; some patients even presented with active hemophagocytosis in macrophages [18]. In this study, only 2 cases (3%) had cutaneous manifestations. The reported low recurrence rate of KD was supported by our finding of a total absence of recurrence. Mortality is also rare [11]; no mortality occurred in this series.

There are no definite laboratory tests available for the diagnosis of KD. White blood cell counts were generally in the normal range in this series, but leukopenia was found in about 29% of study subjects. The presence of leukopenia is compatible with the diagnosis of KD. This disease has often been misdiagnosed as tuberculosis, SLE or malignant lymphoma, which delays treatment and worsens the patient's prognosis [25-29]. In this series, 1 patient with KD had underlying epiglottic carcinoma, and we presumed that a transient immune reaction may have explained this phenomenon [11].

In conclusion, this study of the clinicopathologic features of KD observed in southern Taiwan suggests that physicians should be alert to the possibility of KD when a patient visits the clinic complaining of the development of neck lymphadenopathy.

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