Kikuchi's Disease With Multisystemic Involvement and Adverse Reaction to Drugs

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ABSTRACT. Kikuchi's disease (KD), or histiocytic necrotizing lymphadenitis, was initially described in Japan in 1972. In the following years, several series of cases involving patients of different ages, races, and geographic origins were reported, but pediatric reports have been rare.

The etiology of KD is unknown, although a viral or autoimmune hypothesis has been suggested. The most frequent clinical manifestation consists of local or generalized adenopathy, although in some cases, it is associated with more general symptoms, multiorganic involvement, and diverse analytic changes (leukopenia, elevated erythrocyte sedimentation rate, and C-reactive protein, as well as an increase of transaminases and serum lactic dehydrogenase).

Diagnosis is based on characteristic pathologic findings that permit differentiation of this disease from lymphoma, systemic lupus erythematosus, and infectious lymphadenopathies.

We present here the case of a 14-year-old boy who presented with severe systemic manifestations and transient fulminant hepatic failure in response to treatment with antituberculosis drugs. *Pediatrics* 1999;104(2). URL: http://www.pediatrics.org/cgi/content/full/104/2/e24; *Kikuchi's disease, lymphadenitis, liver failure, antituberculosis drugs.*

ABBREVIATIONS. KD, Kikuchi's disease; LDH, serum lactic dehydrogenase.

CASE REPORT

A 14-year-old white boy was admitted to our hospital after presenting with fever up to 39.8°C for 1 week, malaise, odynophagia, arthralgia, myalgia, abdominal pain, and pruritic skin eruption. Personal and family history was irrelevant. He did not recall any history of exposure to fleas, ticks, cats, or dogs, and there was no indication of animals scratches. On physical examination, several multiple peripheral adenopathies were detected (cervical, axillary, and inguinal), the sizes of which ranged from 0.5 to 2.5 cm in diameter. In general, these nodes were indurated, mobile, and relatively tender. Liver and spleen were palpable 4 cm and 2 cm, respectively, below the costal margin. Erythematous, flat-tipped papules were patent on the face, back, and extremities (Fig 1).

Serial blood analyses during the first 2 weeks after admission revealed pancytopenia (2.7×10^9 leukocytes/L with normal differential formula and atypical lymphocytes in peripheral blood; 9.3 g/dL hemoglobin; 107×10^9/L platelets). Erythrocyte sedimentation rate was 39 mm per hour, and C-reactive protein was 163 mg/dL. Biochemical analysis, coagulation, hepatic and renal functions, immunoglobulins, and complement count were normal (Tables 1, 2). Rheumatoid factor, antinuclear antibodies, direct Coombs test, and two Mantoux test results proved to be negative. Multiple blood, urine, feces, sputum, and tissue culture results also were negative. Antibody titers against Epstein–Barr, cytomegalovirus, hepatitis, HIV, and Parvovirus B_{19}, and serum polymerase chain reaction for herpesvirus type 6 were negative as well, as were results of serologic tests for syphilis, *Brucella*, toxoplasmosis, *Leishmania*, *Rickettsia*, *Borrelia*, and *Bartonella henselae* and *quintana*.

Results of chest roentgenography, echocardiography, and bone scan were normal; an abdominal ultrasound examination detected hepatosplenomegaly with uniform density and nephromegaly with increased cortical echogenicity.

The patient was treated with ceftriaxone and nonsteroid antiinflammatory drugs during the second week of fever. with apparent lack of remission. Furthermore, the condition worsened with an onset of somnolence, headache, and emesis during the third week, potentiated by the detection of aseptic meningitis as certified by cerebrospinal fluid analysis that disclosed 32 leukocytes (90% monocytes), 48 mg/dL protein, and 68 mg/dL glucose.

Biopsy of the bone marrow revealed a normal cellular content. An immunophenotypic study of the marrow and peripheral blood showed an inversion in the CD_4/CD_8 ratio and depletion of B lymphocytes (0.2% of total) (Table 2). However, these tests were not repeated.

Biopsy results of the lymph nodes were compatible with histopathology of histiocytic necrotizing lymphadenitis; ie, they showed wide areas of confluent necrosis in paracortical zones, marked karyorrhexis, crescentic histiocytes and immunoblastic type cells in an absence of neutrophils, and an intact node capsule (Fig 2).

Cutaneous biopsy demonstrated lymphohistiocytic infiltrates, predominantly perivascular, without any necrosis of the adjacent vascular wall.

Into the fourth week of illness, we decided to begin empiric treatment with corticoids (intravenous methylprednisolone, 2 mg/kg per day) and three antituberculosis drugs (isoniazid, rifampicin, pyrazinamide) while awaiting definitive microbiologic test results (tuberculosis infection is common in our country). On the third day of treatment, jaundice, 8 cm hepatomegaly, and a generalized erythematous rash were observed, confirmed as a fulminant hepatic failure (serum glutamic pyruvate transaminase, 1180 U/L; serum glutamic oxalacetic transaminase, 3220 U/L; alkaline phosphatase, 5420 U/L; serum lactic dehydrogenase [LDH], 17 540 U/L; total bilirubin, 4.9 mg/dL; albumin, 2.2 g/dL; international normalized ratio, 2.13; and fibrinogen, 125 mg/dL). No signs of bleeding or encephalopathy were found. Antituberculosis drug therapy was suspended once hepatic failure was detected (3 days in treatment). Hepatic function normalized 1 week later (Table 2).

The patient received intravenous methylprednisolone for 10 days. He was then put on oral prednisone, which was slowly tapered over 3 months. In the sixth week of illness (8 days of corticotherapy), fever, hepatosplenomegaly, and lymphadenopathy receded. Pancytopenia abated in 2 months that followed, whereas arthromyalgia and nephromegaly persisted until 3 months later. A posteriori, after 2 years of follow-up, no symptoms or signs of disease relapse were detected.

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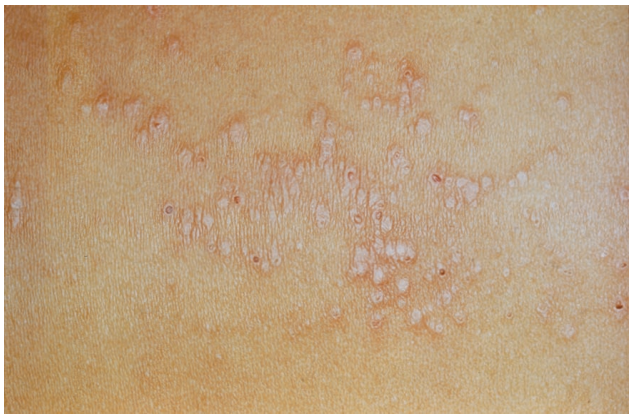

Fig 1. Erythematous papules, ~5 mm in diameter, on the back.

DISCUSSION

KD has been described primarily in people younger than 30 years of age, predominantly in women, and in Asian populations.[1–5] The age range is broad (4–75 years), but only 5% to 10% of patients are younger than 21 years of age.[3–13] In our country, descriptions of KD in the clinical literature are limited to isolated case reports, and only one of these involves a pediatric patient.[9]

The most frequent clinical manifestation of KD is an isolated cervical lymphadenopathy, although other lymphatic regions may be affected. The multiple lymphadenopathy occurs (as in the example of our patient) in 1.3% to 22.2% of cases.[3,5,13] It might be accompanied by other, more variable symptoms that generally consist of fever (30% to 50% of patients), fatigue, musculoskeletal pains, night sweating, loss of weight, and chest and abdominal pain. In the case of unsuspected occult lymphadenopathy, the patient may debut with fever of unknown origin.

Noncharacteristic skin lesions have been observed in ~30% of patients, and usually are described as nodules, papules, maculopapular, disseminated erythema, or urticarial. Cutaneous biopsy results may show diffuse dermal infiltration by apoptotic plasmacytoid monocytes, with perivascular and periadnexal distribution.[14] Our patient had a papular rash, and biopsy revealed similar histopathologic findings.

Hepatosplenomegaly associated with KD has been detected on a relatively frequent basis, whereas nephromegaly was reported previously in only one case of 40-year-old patient with intraabdominal lymph node involvement.[15] Neurologic manifestations are rare and have been described only in iso-

TABLE 1. Immunologic Parameters in Peripheral Blood*

Differential Leukocyte Count		Immunophenotype Peripheral Blood Lymphocyte Surface Markers		Immunoglobulin Levels	
Leukocytes	5.05 × 10^9/L	T-cell markers		IgG	1440 mg/dL
Segmented neutrophils	74%	CD_3	45%	IgA	409 mg/dL
Band cell forms	6%	CD_4	7.5%	IgM	277 mg/dL
Lymphocytes	12%	CD_8	58%	IgE	68 UI/mL
Monocytes	6%	CD_4/CD_8	2%		
Eosinophils	2%	B-cell markers			
		CD_{19}	0.2%		
Atypical lymphocytes		CD_{19}/CD_{10}	0.1%		
Medium and large		CD_{19}/CD_5	0.05%		
Irregularly shaped nuclei					
Abundant bluish cytoplasm		Polyclonal surface immunoglobulins			
		NK-cell markers			
		CD_{56}	7.3%		
		Other markers			
		CD_5	57%		
		CD_{10}	0.3%		

* These tests were performed on 21st day of illness.

TABLE 2. Laboratory Profiles

Day of Illness	Day 7	Day 29	Day 36	Day 56
Blood cell count				
White blood cells (cells × 10^9/L)	2.7	7.1	4.3	11.6
Hemoglobin (g/dL)	9.3	8.3	7.6	11.1
Platelets (cells × 10^9/L)	107	110	188	289
Hepatic function				
Serum glutamic oxalacetic transaminase (U/L)	34	3220	25	21
Serum glutamic pyruvate transaminase (U/L)	38	1180	62	26
Alkaline phosphatase (U/L)	250	5420	630	353
LDH (U/L)	657	17540	810	485
Total bilirubin (mg/dL)	0.3	4.9	1.4	0.8
Albumin (g/dL)	3.8	2.2	4.4	5.2
International normalized ratio	0.93	2.13	1.05	1.01
Fibrinogen (mg/dL)	225	125	180	278

Fig 2. Biopsy specimen from cervical lymph node shows large areas of necrosis in the paracortex (hematoxylin–eosin, original magnification ×25).

lated cases of patients with aseptic meningitis,[10,16] acute cerebellar ataxia,[17] and secondary intracranial hypertension to cervical venal obstruction.[9]

Diagnosis of KD is based on histopathologic observations of lymph node material obtained by fine-needle aspiration or open biopsy.[18] In our case, both methods yielded the same information. The characteristic histopathologic features of the disease are 1) focal necrosis, predominantly in the paracortical region with abundant karyorrhexis; 2) aggregates of atypical mononuclear cells around the zone of necrosis (crescentic histiocytes, plasmacytoid monocytes, and immunoblasts); 3) absence of neutrophils and paucity of plasma cells; and 4) usually intact lymph node capsule. The histologic differential diagnosis of KD includes other causes of necrotizing lymphadenitis including infectious (tuberculosis, toxoplasmosis, yersiniosis, cat scratch disease); autoimmune (systemic lupus erythematous, Kawasaki's disease); and neoplastic diseases (lymphoma). In the present case, results of a thorough microbiologic examination proved negative, and lack of analytic results that would suggest autoimmune reaction helped diagnose KD. An immunophenotypic study of peripheral blood, bone marrow, and lymph nodes is useful for differentiating this type of malignant lymphoproliferative processes. It is characterized by predominance of T lymphocytes infiltrations belonging to the CD_8 subtype, with frequent and typical inversion of the CD_4/CD_8 ratio.[19] The results obtained from the immunophenotypic study of peripheral blood and bone marrow performed on our patient were compatible with these references.

The pathogenesis of KD is still unknown. However, the clinical presentation and histiologic changes suggest hyperimmune reaction of T cells, activated by an unidentified pathogen.[3,4] At present, it remains to be seen whether the immune response is initially sparked by an infectious agent or whether it reflects some underlying intrinsic defect of T cell immunity.[14] The association of several infectious agents including bacteria (*Brucella*, *Yersinia*), parasites (toxoplasmosis), and viruses (Epstein–Barr, herpesvirus 6, Parvovirus B_{19}) was suggested, but thus far, no etiologic relationship has been confirmed.[20] The importance of autoimmune mechanisms in the pathogenesis of the disease has been demonstrated by the description of patients who developed connective tissue diseases (systemic lupus erythematous, Still's disease) before or after being diagnosed with histiocytic necrotizing lymphadenitis.[21,22] Moreover, the majority of patients do not develop autoimmune dysfunction, although the presence of positive antinuclear antibodies, rheumatoid factor, and direct Coombs results have been reported.[3,10,14] In our patient, the determinations noted above were negative.

The most frequent analytic alterations in KD include leukopenia with neutropenia, anemia, and the presence of atypical lymphocytes in peripheral blood[5]; therefore, pancytopenia observed in our patient was by all standards, exceptional.[19] An increase in reagents of acute phase and LDH often are reported. Subsequently, a moderate increase in the level of transaminases has been described in the cases that are accompanied by the alteration of hepatic function.[10,23] Hepatic failure in our patient can be interpreted as an extremely early adverse reaction to antituberculosis drugs. The possibility that the severe liver dysfunction described previously could have occurred in the absence of antituberculosis drugs cannot be excluded, but this seems unlikely given that hepatic function was normal before the drug therapy. The mechanisms of drug-induced hepatotoxicity resulting from antituberculosis agents are thought to involve direct cytotoxicity (by the drugs or its metabolites). Nonetheless, they are not yet fully discerned. An immune-related component is also believed to play a role, because several authors have documented or suggested immunologic effects.[24,25] In view of our findings, we speculate that fulminant hepatic failure may have been expedited by the underlying hyperimmune reaction. This stems from the fact that, thus far, no case of KD with fulminant hepatic failure or with an adverse reaction to drugs has been reported.[26]

Although two fatal cases of KD have been documented,[12,27] spontaneous improvement and disappearance of symptoms are frequently the norm, usually within 1 to 6 months of initial onset. In 3% of patients, the disease may recur for many years.[4,5] No treatment is necessary, and nonsteroidal antiinflammatory drugs are helpful in alleviating fever and the tenderness of lymph nodes. The use of corticosteroids has been recommended to prevent death, but only in severe cases with hyperpirexia, aseptic meningitis, or cerebellar ataxia. The aforementioned therapy also is reserved for cases with an important increase in LDH or antinuclear antibodies titer.[10,17,27]

By and large, our patient's clinical profile reflects a severe case of KD, with important constitutional symptoms, exceptional systemic manifestations (rare pancytopenia and nephromegaly), and ensuing complications (aseptic meningitis and hepatic failure). It is also important to note that in previous studies, an adverse reaction to drugs and fulminant hepatic failure have not been associated with this disease.

REFERENCES

1. Kikuchi M. Lymphadenitis showing focal reticulum cell hyperplasia with nuclear debris and phagocytosis. *Nippon Ketsueki Gakkai Zasshi*. 1972;35:379–380
2. Fujimoto Y, Kozima Y, Yamaguchi K. Cervical subacute necrotizing lymphadenitis. A new clinicopathologic agent. *Naika.* 1972;20:920–927
3. Dorfman RF, Berry GJ. Kikuchi's histiocytic necrotizing lymphadenitis: an analysis of 108 cases with emphasis on differential diagnosis. *Semin Diagn Pathol*. 1988;5:329–345
4. Tsang WY, Chan JKC, Ng CS. Kikuchi's Lymphadenitis. A morphologic analysis of 75 cases with special reference to unusual features. *Am J Surg Pathol*. 1994;18:219–231
5. Kuo T. Kukuchi's disease (histiocytic necrotizing lymphadenitis). A clinicopathologic study of 79 cases with an analysis of histologic subtypes, immunohistology and DNA ploidy. *Am J Surg Pathol*. 1995;19: 798–809
6. Rudin C, Werlin R, Rutishauser M, Ohnacker H. Mesenterial histiocytic necrotizing lymphadenitis. *Helv Pediat Acta.* 1987;42:35–40
7. Smith HL. Necrotizing lymphadenitis (Kikuchi's disease). *Pediatrics*. 1993;91:152
8. Boyce TG, Moffet HL, Roh SK, Desouky SS. Pathological cases of the month. Kikuchi's disease (histiocytic necrotizing lymphadenitis). *Arch Pediatr Adolesc Med.* 1994;148:427–428
9. Calvo I, Andreu E, Roman J, Tio MD, Donat J, Villanueva A. Enfermedad de Kikuchi o linfadenitis necrotizante histiocitaria. *An Esp Pediatr.* 1995;42:213–214
10. Debley JS, Rozansky DJ, Miller ML, Katz BZ. Histiocytic necrotizing lymphadenitis with autoimmune phenomena and meningitis in a 14-year-old girl. *Pediatrics*. 1996;98:130–133
11. Heldenberg D, Amar M, Ben-Arie Y, Iuchtman M. Axillary involvement in pediatric Kikuchi's disease. *Eur J Pediatr Surg*. 1996;6:32–34
12. Norris AH, Krasinskas AM, Salhany KE, Gluckman SJ. Kikuchi–Fujimoto disease: a benign cause of fever and lymphadenopathy. *Am J Med*. 1996;171:401–405
13. Pileri S, Kikuchi M, Helbron D, Lennert K. Histiocytic necrotizing lymphadenitis without granulocytic infiltration. *Virchows Arch [A].* 1982;395:257–271
14. Aqel N, Henry K, Woodrow D. Skin involvement in Kikuchi's disease: an immunocytochemical and immunofluorescence study. *Virchows Arch.* 1997;430:349–352
15. Tsujino I, Oguma Y, Yamaguchi J. Involvement of the intraabdominal lymph nodes in a case of subacute necrotizing lymphadenitis. *Rinsho-Ketsueki.* 1993;34:937–941
16. Atarashi K, Yoshimura N, Nodera H, Tsukimoto K, Beppu H, Kanayama M. Recurrent histiocytic necrotizing lymphadenitis (Kikuchi's disease) in an human T lymphotropic virus type I carrier. *Intern Med.* 1996;35:821–825
17. Nagata A, Shoji H, Kaji M. A case of subacute necrotizing lymphadenitis with acute cerebellar ataxia. *Rinsho Shinkeigaku*. 1986;26:354–357. (In Japanese)
18. Tsang WY, Chan JK. Fine-needle aspiration cytologic diagnosis of Kikuchi's lymphadenitis. A report of 27 cases. *Am J Clin Pathol*. 1994;102: 454–458
19. Lima M, Silvestre F, Correia J, Oliveira J, Justiça B. Kikuchi's disease: a case report with emphasis on flow cytometric studies. *Sangre*. 1996;41: 383–386
20. Hollingsworth HC, Peiper SC, Weiss LM, Raffeld M, Jaffe ES. An investigation of the viral pathogenesis of Kikuchi–Fujimoto disease. Lack of evidence for Epstein-Barr virus or human herpesvirus type 6 as the causative agents. *Arch Pathol Lab Med.* 1994;118:134–140
21. Eisner MD, Amory J, Mullaney B, Tiemey L Jr, Browner WS. Necrotizing lymphadenitis associated with systemic lupus erythematosus. *Semin Arthritis Rheum.* 1996;26:477–482
22. Lyberatos C. Two more cases of Still's disease and Kikuchi's. *J Rheumatol.* 1990;17:568–569
23. Bailey EM, Klein NC, Cunha BA. Kikuchi's disease with liver dysfunction presenting as fever of unknown origin. *Lancet*. 1989;21:986. Letter
24. Olle Goig JE. A rare case of hypersensitivity to multiple antituberculosis drugs. *Int J Tuberc Lung Dis*. 1997;1:191. Letter
25. Ungo JR, Jones D, Ashkin D, et al. Antituberculosis drug-induced hepatotoxicity. The role of hepatitis C virus and the human immunodeficiency virus. *Am J Respir Crit Care Med.* 1998;157:1871–1876
26. Yoo JH, Choi JH, Kim YR, Shin WS, Kang MW. Kikuchi–Fujimoto disease: benign cause of fever and lymphadenopathy. *Am J Med*. 1997; 103:332–334. Letter
27. Shih-Hua L, Wang-Sheng K, Herng-Sheng L, Wei-Shou H. Kikuchi's disease associated with lupus-like syndrome—a fatal case. *J Rheumatol*. 1992;19:1995–1996. Letter

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