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**KIKUCHI'S LYMPHADENOPATHY
A RELATIVELY RARE BUT IMPORTANT
CAUSE OF LYMPHADENOPATHY IN GREECE,
POTENTIALLY ASSOCIATED WITH
THE ANTIPHOSPHOLIPID SYNDROME**

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ABSTRACT

Kikuchi-Fujimoto disease is a form of reactive lymphadenopathy, which was firstly described in Japan, but is uncommon in the Western world. We retrospectively reviewed the medical records of 9 cases of adult or adolescent Kikuchi's disease diagnosed in a single Haematology Unit in Athens, Greece between 1990 and 2006. The median age of the patients was 25 years (14-40) and 8/9 were females. All patients presented with cervical lymphadenopathy sparing the supraclavicular fossa; one had associated axillary lymphadenopathy, 7 had fever and 2 were asymptomatic. The median duration of lymphadenopathy before presentation was 30 days (10-45). Just palpable splenomegaly was recorded in 3 patients. The median value of the maximal lymph node diameter was 2 cm (1-5) and only 1/9 had nodes >2 cm in their largest diameter. Lymphadenopathy was tender in 2 patients; hard nodes were observed in 3. The median leukocyte count was $4.7 \times 10^9/l$ (2.2-4.9) with a normal differential in 7/9 patients. No infectious agent could be demonstrated. One patient however had clinical and laboratory evidence of primary antiphospholipid syndrome (APLS). In conclusion, Kikuchi's disease represents a rare but important diagnostic possibility for patients presenting with lymphadenopathy in Greece and other Western countries. In this setting, autoimmune disorders, mainly lupus and APLS, should be considered and excluded by the appropriate laboratory work-up.

Keywords: Kikuchi's disease, Kikuchi-Fujimoto, lymphadenopathy, cervical, antiphospholipid syndrome, autoimmune disease

INTRODUCTION

Kikuchi-Fujimoto disease is an uncommon form of reactive lymphadenopathy, which was firstly described in Japan in 1972 [1, 2]. Since then it has been recognized in many other countries worldwide as a self-limited syndrome characterized by lymphadenopathy [3, 4, 5, 6]. It usually affects young females presenting with localized -predominantly cervical- lymphadenopathy, which is frequently associated with fever. The diagnosis is based on the histologic findings. The histologic picture is characterized by karyorrhectic foci, usually with coagulative necrosis without neutrophilic infiltration, and the presence of histiocytes and immunoblasts [3]. It may resemble to that observed in systemic lupus erythematosus (SLE), but may also be misdiagnosed as malignant lymphoma [3, 7]. An association between Kikuchi's lymphadenopathy and SLE or other autoimmune condition has been reported in some cases. In this study we present our experience with this rare disorder in a single center in Greece.

PATIENTS AND METHODS

We report 9 cases of Kikuchi's disease diagnosed in the Haematology Unit, First Department of Internal Medicine, Athens University from 1990 to 2006 in adult or adolescent patients. Four of these cases were part of a series of 516 consecutive patients with lymphadenopathy, which has been previously published [8]. During the same period there was also an additional case of SLE, who reported a history of Kikuchi's disease 7 years prior to her presentation. The clinical and laboratory features of this case were not available and were not included in this analysis.

Demographic, clinical, and laboratory data were extracted from the medical records of the patients. The diagnosis was based on lymph node histological examination in all cases. All patients underwent laboratory testing with complete blood count and differential, chest X-rays, Epstein-Barr virus (EBV), cytomegalovirus (CMV) and Toxoplasma gondii serology. Most patients were also tested for erythrocyte sedimentation rate (ESR), biochemical profile, serum protein electrophoresis and the presence of rheumatoid factor, antinuclear and anti-ds DNA antibodies as well as serum complement levels. Other tests were performed in less than half of the patients. Computed tomography and bone marrow biopsy were not routinely performed. Clinically significant anemia was defined as hemoglobin levels <115 g/l, while clinically significant thrombocytopenia as platelet counts $<100 \times 10^9$ /l. Leucopenia was defined as white blood cell count $< 4 \times 10^9$ /l and neutropenia as an absolute neutrophil count of less than 1.8×10^9 /l, while lymphocytopenia was defined as an absolute lymphocyte count of less than 1.5×10^9 /l.

RESULTS

Clinical, Laboratory and Histologic Findings

The demographic, clinical and laboratory data of the patients are summarized in tables 1-3. Seven patients were native Greeks, one was Phillipinian and one Kenyan. Both non-Greek patients were living in Greece for more than 10 years. The median age of the patients was 25 years (14-40) and 8/9 of them (89%) were females. All patients presented with cervical lymphadenopathy, 7 patients had fever (78%; in one case low grade only), while 2 were asymptomatic and presented with incidentally discovered lymphadenopathy. The median duration of lymphadenopathy before presentation was 30 days

(range 10-45). Splenomegaly was recorded in 3 patients (33%), but the spleen was just palpable below the left costal margin in all 3 cases. One patient had palpable mild hepatomegaly, confirmed by ultrasonography. Each one of fatigue, sorethroat, sweats, arthralgias and headache was reported by 2 patients, while a rash was recorded in a single case.

Cervical lymphadenopathy was observed in all 9 patients, being unilateral in 5 (left 2; right 3) and bilateral in 4 cases. The submandibular lymph nodes were involved in 3 cases. Supraclavicular nodes were not enlarged in any case. Eight patients had lymphadenopathy restricted to the cervical areas, while a single patient had bilateral axillary lymph nodes up to 1x1 cm, which resolved later. The median value of the maximal lymph node diameter 2 cm (range 1-5 cm), but only one out of the 9 patients had lymph nodes greater than 2 cm in their maximal diameter. Lymphadenopathy was tender in 2 (out of 7) patients. Hard lymph nodes were observed in 3 (out of 8) patients.

According to the clinical prediction rule published by our group [9], only a single patient was considered to be in need of lymph node biopsy. This was due to the large size (5cm) and the hard texture of the neck mass in patient #3. However, all patients finally underwent a lymph node biopsy. This decision was based on empirical clinical judgment, in order to reach the diagnosis of Kikuchi's disease, due to prolonged non-remitting lymphadenopathy,. Briefly the histologic findings of the 9 cases were as follows: Lymph node architecture was completely effaced in 3 and partially preserved in 6 cases. Necrosis was present in all cases (patchy in 7 and confluent in 2), associated with apoptotic cells and nuclear karyorrhectic debris. Aggregates of histiocytes were observed in all cases (numerous in 7/9) as well as activated

T-lymphocytes (numerous in 4/9) and plasmacytoid monocytes. Neutrophils and eosinophils were not observed in any case.

The median leukocyte count was $4.7 \times 10^9/l$ (2.2 - 4.9); all patients had low or low-normal leukocyte counts. Leucopenia or low-normal leukocyte counts with normal differential were recorded in 7 patients. The remaining two patients presented with inversion in differential leukocyte counts. The median neutrophil count was $1.7 \times 10^9/l$ (1.1-3.2); 5/9 patients (56%) had neutropenia. The median lymphocyte count was $1.6 \times 10^9/l$ (0.8-2.9); 4/9 (44%) patients had lymphocytopenia. Clinically significant anemia was observed in 3 patients (33%). No case of clinically significant thrombocytopenia was observed. The median ESR was 51.5 mm/h (5-65), and ESR was ≥ 30 mm/h in 6/8 patients (75%). Serum lactate dehydrogenase (LDH) levels were elevated in 4/6 (67%) patients and elevated aminotransferase levels were recorded in 2/6 (33%) patients. However, in patient #9 the clinical course was complicated by significant transaminasemia (5-10x), which led to a non-diagnostic liver biopsy, despite the normal initial transaminase levels. Polyclonal hypergammaglobulinemia was observed in 4/8 patients (50%). The hematologic and biochemical findings in this series of patients with Kikuchi's disease are summarized in table 2. Baseline chest X-rays did not reveal abnormal findings in any case, although patient #9 developed severe pneumonia and pleuritis due to *Pseudomonas aeruginosa* during her hospitalization, which resolved with the appropriate antimicrobial treatment. Serum tests for current infection by Epstein-Barr virus (VCA-EBV) and cytomegalovirus were performed in all patients, and were consistently negative (table 3). Among 9 patients, 8 had no evidence of current toxoplasmic infection and one had a stable IgM titer of 1/150 with negative

IgG. This was considered as a false positive result. Other serological tests for various infectious agents, including herpes simplex and *Yersinia enterocolitica*, were negative, when performed (table 3).

Serological workup for autoimmune disorders is also summarized in table 3. Two patients tested positive for antinuclear antibodies at titers 1/80 speckle and 1/160 diffuse. The former patient (#8) had a borderline anti-dsDNA result and a positive IgM anticardiolipin (41.3, 57.3, and 41 vs. normal limit <12.5 MPLU/ml, in serial measurements over 14 months) and β_2 -GPI assay (39.4 vs normal limit <15), while the initially normal IgG anticardiolipin increased later on (9.9 and 38 vs. normal limit <15 GPLU/ml). Lupus anticoagulant was negative. This patient had also marked polyclonal hypergammaglobulinemia. During the evaluation of febrile lymphadenopathy she also developed thrombosis of the superior vena cava, while she had reported a history of 2 consecutive spontaneous abortions. A subsequent work-up for thrombophilia was negative. Thus a diagnosis of primary antiphospholipid syndrome (APLS) was established [10], since she did not fulfill the diagnostic criteria for SLE. At 1-year follow-up visit she is afebrile, with persistent serologic abnormalities, but no evidence of SLE. In the second patient (#9) antinuclear antibodies disappeared after the resolution of Kikuchi's lymphadenopathy, while she did not fulfill the diagnostic criteria for SLE at any timepoint.

Follow up

In all patients lymphadenopathy resolved without specific treatment. None of the patients developed SLE during the initial observation phase, usually of 6-12 month duration. Long term follow-up beyond this phase was available for 4 patients (excluding the recent patient #9), all of whom were in excellent

clinical condition at a median of 8.5 years after the diagnosis (range 2.5-15). Cases of recurrent Kikuchi's disease or comorbid conditions have not been observed, with the exception of the synchronous antiphospholipid syndrome in patient #8, and the Pseudomonas pneumonia which complicated the clinical course of patient #9.

DISCUSSION

Although Kikuchi's lymphadenopathy was originally described in Japan 35 years ago, it has been reported worldwide during the last 15 years [1, 2, 3, 4, 5, 6]. The true incidence of Kikuchi's lymphadenopathy in unselected series of adult patients presenting with lymphadenopathy is not known. Figures up to 5.7% of all lymph node biopsies have been reported in Asia, reflecting the increased local incidence of the disease, but actually refer to highly selected populations of patients with clinically significant lymphadenopathy requiring a lymph node biopsy [11]. Published experience with Kikuchi's disease in Greece is limited [4]. Among 9 patients presented here, 4 had been part of a series of 516 consecutive, unselected, patients, who presented with lymphadenopathy in a single Haematology Unit [8]. On the basis of these data, the estimated frequency of Kikuchi's disease was 0.8% among patients presenting with lymphadenopathy in a teaching hospital in Greece. **However the self-limited course of the disease may lead to underestimation of its true incidence, since, in an unknown fraction of patients, the disease may resolve prior to the final decision to perform a lymph node biopsy.**

The etiology of Kikuchi's lymphadenopathy remains unknown. Several infectious agents have been proposed as potential causes of the disease but clear evidence is lacking. On the basis of serologic findings Kikuchi's lymphadenopathy has been associated with *Toxoplasma gondii*, *Yersinia enterocolitica*, HTLV-1, and hepatitis C virus, while EBV and human herpesvirus-6 and 8 (HHV-6 and HHV-8) have been detected by polymerase chain reaction or in situ hybridization [3,12]. Rubella, brucellosis and parvovirus B19 have also been associated with Kikuchi's disease [3,13]. However all these associations are either rare or have not been confirmed by alternative laboratory methods. In the present series there was no serologic evidence for the implication of infectious agents in the pathogenesis of the disease, as shown in table 3. It must be stressed out that the reported *Pseudomonas pneumonia* was not considered as the cause of Kikuchi's disease in patient #9. We rather believe that it was a complication of the disease, which was already present for almost 45 days.

In a review of 108 predominantly American cases of Kikuchi's lymphadenopathy [7] the median age was 30 years, almost 95% of the patients were younger than 40 years, and the male to female ratio was 1:4. Fever complicated the clinical picture in 39% of the patients, weight loss and sweats in 10-15% of the patients, but other symptoms, except of local ones, were recorded with frequencies of less than 5%. The mean duration of the symptoms was 3 months (range 1-24). In 81% of the patients lymphadenopathy was localized, in 14% it was limited to two sides, and was more generalized in only 6% of the patients.

In another report of 58 patients from Taiwan [14] the mean age was 25 years and the male to female ratio was 1:1.76. Fever complicated the clinical picture

in 43% of the patients, sore throat was recorded in 21%, but weight loss and night sweats were very rare (3% and 2% of the patients respectively). The median duration of symptoms was 4 weeks. All patients had cervical lymphadenopathy (usually posterior and 21% bilateral) and only 5% had axillary lymphadenopathy. Thus approximately 95% of the patients had 1 or 2 involved nodal sites. Small nodes, <2 cm, were recorded in 75% of the patients (range 0.5-9 cm) and tenderness in 50%, while splenomegaly was very rare (3%).

Our data confirm that patients suffering from this self-limited condition are mainly young females, presenting with predominantly cervical lymphadenopathy sparing the supraclavicular fossa. The disease is frequently febrile. Leucopenia or low-normal leukocyte counts with normal differential are the rule. Although not diagnostic, this combination of the demographic, clinical and laboratory features should raise the suspicion of Kikuchi's disease in patients with unexplained lymphadenopathy. The marked predilection to the involvement of cervical lymph nodes and the young age of the patients is clear [7, 14]; however female predominance may be less prominent in Asia than in Europe or USA [14].

The diagnosis of Kikuchi's disease is based on the histologic findings. **Histological examination reveals partial maintenance of the lymph node architecture, with the presence of reactive germinal centers in residual follicles. There are patchy areas of irregularly shaped necrosis, which is occasionally confluent. The necrosis consists of eosinophilic fibrinoid deposits including nuclear fragments and is surrounded by large accumulations of histiocytes, phagocytosing the aforementioned cellular debris. These areas of histiocytic aggregates also include small lymphocytes, activated large T**

lymphocytes, scarce plasma cells and nests of plasmacytoid monocytes. The consistent absence of neutrophils and eosinophils, as in our cases, is a distinctive feature of Kikuchi's disease. Reliable cytological diagnosis has been reported in half of the patients in one study, but it cannot substitute lymph node biopsy [15]. All of our patients actually underwent a lymph node biopsy. Based on the clinical prediction rule published by our group [9], only 1 patient fulfilled the criteria to undergo a lymph node biopsy, while in the remaining patients the decision was made on the basis of clinical judgment, due to the presence of "suspicious", persistent, unexplained lymphadenopathy. This clinical prediction rule was developed in order to facilitate the differentiation between serious and non-serious lymphadenopathy. In this sense failure to classify patients with Kikuchi's disease in the group of patients predicted to be in need of biopsy is consistent with the benign, "non-serious" nature of the disease.

From the clinical point of view, Kikuchi's lymphadenopathy raises problems of differential diagnosis, because of its subacute presentation with a picture reminiscent of Hodgkin's or non-Hodgkin's lymphoma, dominated by limited, usually cervical lymphadenopathy in febrile patients with elevated ESR. However the absence of supraclavicular lymphadenopathy and mediastinal enlargement, the frequently small size of enlarged nodes (less than or equal to 2 cm in all but one case in this study), the low or low-normal leukocyte count with normal differential and the absence of other cytopenias or thrombocytosis may facilitate the clinical distinction between lymphoma and Kikuchi's disease in most cases. Extensive diagnostic work-up with computed tomography, bone marrow biopsy or other tests beyond that needed for the

clarification of the cause of lymphadenopathy is not justified for the vast majority of cases of Kikuchi's disease.

At the histologic level the presence of T-immunoblasts, occasionally bearing atypical morphologic features, in Kikuchi's disease may result to confusion with aggressive non-Hodgkin's lymphomas, mainly of the T-cell phenotype. CD8+ cells predominate in Kikuchi's disease, while the majority of the T-cell lymphomas are CD4+ rather CD8+. Clues for the differential diagnosis between the two entities are given in table 4. The presence of fever with low nodal "disease burden" and the whole clinical picture may help to avoid such misinterpretations.

Another clinical problem is the reported association with SLE [3, 16, 17, 18, 19]. Several authors have reported the association between Kikuchi's disease and SLE. In a review of 35 cases SLE developed after the diagnosis of Kikuchi's disease in 14 and concomitantly with the disease in 14, while Kikuchi's developed after SLE in 7 patients [20]. Thus SLE should carefully be excluded both serologically and histologically in every patient with Kikuchi's disease. SLE-associated lymphadenopathy can be histologically differentiated from Kikuchi's disease on the basis of the presence of hematoxylin bodies, neutrophils, vasculitic lesions, the Azzopardi phenomenon and the abundance of plasma cells (see table 4). However these clear features may not always be present, leading to diagnostic problems. Whether SLE really complicates the course of a small minority of patients with Kikuchi's lymphadenopathy or these cases actually represent examples of misdiagnosis at the initial presentation of SLE with lymphadenopathy is unclear [3]. However, although the clinical findings usually resolve rapidly, prolonged follow-up is needed

after a diagnosis of Kikuchi's lymphadenopathy has been established, in order to detect rare cases, who might develop SLE.

In our series SLE did not develop in any patient after the diagnosis of Kikuchi's disease. It must be pointed out that during the study period, one patient presented with SLE and reported an episode of Kikuchi's lymphadenopathy 7 years prior to the diagnosis. This patient was not included in the study because there was no histologic verification available to confirm that the patient had indeed Kikuchi's disease and not lupus lymphadenitis. However 2/7 patients tested had positive antinuclear antibodies and 1/3 tested had antithyroid antibodies, suggesting a relation of Kikuchi's disease with autoimmunity, which is more clearly shown in previously reported studies. In this context, one of the 9 patients reported here actually had primary APLS, which was diagnosed concomitantly with Kikuchi's lymphadenopathy. This patient did not fulfill the diagnostic criteria for SLE. There are 3 recent additional case reports linking Kikuchi's lymphadenopathy with the APLS, either primary or secondary to SLE [21, 22, 23]. Thus the APLS should also be looked for in patients with Kikuchi's lymphadenopathy, since it may coexist with Kikuchi's disease.

In conclusion, Kikuchi's disease represents a rare but important diagnostic possibility for patients presenting with lymphadenopathy in Greece and other Western countries. The wider recognition of this self-limited entity would result to less extensive diagnostic work-up, appropriate testing for possible underlying autoimmune disease (mainly SLE, but also APLS and probably other entities), avoidance of hospitalization and proper medical consultation regarding the required follow-up.

REFERENCES

1. Fujimoto Y, Kozima Y, Yamaguchi K. (1972) Cervical subacute necrotizing lymphadenitis. A new clinicopathological entity. *Naika* 30: 920-7
2. Kikuchi M. (1972) Lymphadenitis showing focal reticulum cell hyperplasia with nuclear debris and phagocytes. *Acta Hematol Jpn* 35: 379-80
3. Bosch X, Guilabert A, Miquel R, Campo E. (2004) Enigmatic Kikuchi-Fujimoto disease. A comprehensive review. *Am J Clin Pathol* 122: 141-52.
4. Charalabopoulos K, Papalimneou V, Charalabopoulos A, Chaidos A, Bai M, Bourantas K, Agnantis N. (2002) Kikuchi-Fujimoto disease in Greece. A study of four cases and review of the literature. *In Vivo*. 16: 311-6.
5. Norris AH, Krasinskas AM, Salhany KE, Gluckman SJ. (1996) Kikuchi-Fujimoto disease: A benign cause of fever and lymphadenopathy. *Am J Med* 171: 401-5
6. Papadimitriou CS, Papaharalampous NX. (1985) Histiocytic necrotizing lymphadenitis without granulocytic infiltration. *Arch Pathol Lab Med* 109: 107-8
7. Dorfman RF, Berry GJ. (1988) Kikuchi's histiocytic necrotizing lymphadenitis: an analysis of 108 cases with emphasis on differential diagnosis. *Semin Diagn Pathol* 5: 329-45
8. Pangalis GA, Vassilakopoulos TP, Boussiotis VA, Fessas Ph. (1993) Clinical approach to lymphadenopathy. *Semin Oncol* 20: 570-82
9. Vassilakopoulos TP, Pangalis GA. (2000) Application of a prediction rule to select which patients presenting with lymphadenopathy should undergo a lymph node biopsy. *Medicine (Baltimore)* 79: 338-47
10. Levine JS, Branch W, Rauch J. (2002) The antiphospholipid syndrome. *N Engl J Med* 346: 752-63

11. Kuo TT. (1995) Kikuchi'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* 19: 798-809
12. Papadopoulou D, Vergos I, Zacharakis M, Fotiou K. (2005) Kikuchi-Fujimoto's disease in a male with HCV infection. *Haema* 8: 657-9
13. Charalabopoulos K, Papalimneou V, Charalabopoulos A, Bai M, Agnantis N. (2003) *Brucella melitensis* infection stimulates an immune response leading to Kikuchi-Fujimoto disease. *In Vivo* 17: 51-3
14. Yu HL, Lee SS, Tsai HC, Huang CK, Chen YS, Lin HH, Wann SR, Liu YC, Tseng HH. (2005) Clinical manifestations of Kikuchi's disease in southern Taiwan. *J Microbiol Immunol Infect.* 38:35-40
15. Viguer M, Jimenez-Heffernan JA, Perez P, Lopez-Ferrer P, Gonzalez-Peramato P, Vicandi B. (2001) Fine-needle aspiration cytology of Kikuchi's lymphadenitis: A report of ten cases. *Diagn Cytopathol* 25: 220-4
16. El-Ramahi KM, Karrar A, Ashraf Ali M. (1994) Kikuchi disease and its association with systemic lupus erythematosus. *Lupus* 3: 409-11
17. Hu S, Kuo TT, Hong HS. (2003) Lupus lymphadenitis simulating Kikuchi's lymphadenitis in patients with systemic lupus erythematosus: A clinicopathological analysis of six cases and review of the literature. *Pathol Int* 53: 221-6
18. Tumiatu B, Bellelli A, Portioli I, Prandi S. (1991) Kikuchi's disease in systemic lupus erythematosus: an independent or dependent event? *Clin Rheumatol* 10: 90-3
19. Vila LM, Mayor AM, Silvestrini IE. (2001) Therapeutic response and long-term follow-up in a systemic lupus erythematosus patient presenting with Kikuchi's disease. *Lupus* 10: 126-8

20. Santana A, Lessa B, Galrao L, Lima I, Santiago M. (2005) Kikuchi-Fujimoto's disease associated with systemic lupus erythematosus: case report and review of the literature. *Clin Rheumatol* 24: 60-3
21. Chen HC, Lai JH, Huang GS, Gao HW, Chen CH, Kuo SY, Chang DM. (2005) Systemic lupus erythematosus with simultaneous onset of Kikuchi-Fujimoto's disease complicated with antiphospholipid antibody syndrome: a case report and review of the literature. *Rheumatol Int.* 25: 303-6..
22. de Larranaga GF, Remondino GI, Forastiero RR, Cunto ER, Narbaitz M, Olenchuk AB, Zala NS, San Juan JA. (2005) Catastrophic antiphospholipid syndrome and Kikuchi-Fujimoto disease: the first case reported. *Lupus* 14: 967-9
23. Papaioannou G, Speletas M, Kaloutsi V, Pavlitou-Tsiontsi A. (2002) Histiocytic necrotizing lymphadenitis (Kikuchi-Fujimoto disease) associated with antiphospholipid syndrome: case report and literature review. *Ann Hematol* 81: 732-5

Table1: Clinical and Laboratory Features of 9 patients with Kikuchi's Lymphadenopathy

Patient (#)	Year of diagnosis	Sex/Age	Symptoms	Duration of history	Involved nodal sites	Maximal node diameter	Spleno megaly	Leukocytes (x10 ⁹ /l)			Leukocyte differential count
								Total	Neutrophils	Lymphs	
1	1991	F/26	No (incidental LA)	1 mo	Cervical (L)	1 cm	no	4.8	2.6	1.8	normal
2	1992	M/28	Incidental LA Fever up to 38.5°C Mild sorethroat, fatigue	25d 9d	Cervical (R) Submandibular (L)	1.5 cm	no	4.7	3.2	1.3	normal
3	1992	F/24	LA Fever up to 38°C Sweats	10d 10d 10d	Cervical (R)	5 cm	no	4.7	2.7	1.8	normal
4	1993	F/20	No (Incidental LA)	45d	Cervical (L)	1.5 cm	yes*	4.9	2.5	1.8	normal
5	1998	F/25	LA Fever up to 38.5°C	1mo 1w	Cervical (Bil)	1.5 cm	no	2.6	1.4	1.0	normal
6	1999	F/14	LA Fever (recurrent) rash	15d 1 mo	Cervical (R)	2 cm	no	2.5	1.3	1.0	normal
7	2000	F/18	LA Fever (low grade)	45d ?	Cervical (R) Submandibular (B)	2 cm	yes*	4.7	1.7	2.9	inverted
8	2004	F/40	LA Fever up to 38°C Sweats, arthralgias, headache	1mo 1mo	Cervical (R)	2 cm	no	3.7	1.5	1.6	inverted
9	2006	F/34	LA Fever up to 38.4°C Mild sorethroat, fatigue, arthralgias, headache	10d 25d	Cervical (Bil) Sabmandibular (L) Axillary (Bil)	2 cm	yes*	2.2	1.1	0.8	normal

LA = Lymphadenopathy, *spleen just palpable below the left costal margin

Table 2: Summary of non specific laboratory findings in 9 patients with Kikuchi's lymphadenopathy (leukocyte counts and differential are reported in table 1)

Laboratory test	Tested (#)	Abnormal	
		(#)	(%)
Blood Counts			
Hemoglobin < 115 g/l	9	3*	33
Platelets < 140 × 10 ⁹ /l	9	1**	11
ESR ≥ 30mm (1 st hour)	8	5	63
↑ γ-globulins (polyclonal)	8	4	50
Serum LDH (elevated) ‡	6	4	67
ALT/AST (elevated) ‡	6	2	33
Alkaline phosphatase (ALP) /γ-glutamyltranspeptidase (γGT) (elevated) ‡	6	0	0

* Only a single case with hemoglobin levels < 10 g/dl (9.8g/dl)

** 126 × 10⁹/l

‡ above the upper normal limit of the laboratory

Table 3: Summary of work-up for infectious and autoimmune diseases in 8 patients with Kikuchi's lymphadenopathy

Infectious Disease Serological Work up ^{*§}	Tested (#)	Abnormal (#)	Autoimmune Disease Work up [§]	Tested (#)	Abnormal (#)
EBV-VCA	9	0	Antinuclear antibodies	7	2 [¶]
CMV	9	0	Anti-ds DNA	7	1 [¶]
Toxoplasma gondii	9	1 ^{**}	Rheumatoid factor	7	0
Herpes Simplex	5	0	Serum complement (C ₃ , C ₄)	5	0
Yersinia Enterocolitica	4	0	ENA	4	0
Wright test	3	0	Antimicrosomal/Antithyroglobulin antibodies	3	1
			Anticardiolipin IgM	2	1
			IgG	2	1

[¶] 1/80 speckled and 1/160 diffuse, anti-dsDNA 7.5 (max 7.0)

*Abnormal results were considered those, which were indicative of current infection

** This was a false-positive result, as described in the body of the text

§ HHV-6, Parvo-B19, Q-fever, RSV, Adenoviruses, Mycoplasma, Leishmania donovani, HBV, HCV, Mumps, Measles, AMA, Scl-70, pANCA, c ANCA were performed in 1 or 2 cases each and were negative

Table 4: A summary of the differential diagnosis of Kikuchi's disease from non-Hodgkin T-cell lymphomas and Systemic Lupus Erythematosus.

	T-Non Hodgkin's Lymphoma	Kikuchi's Disease	Systemic Lupus Erythematosus
Clinical-Laboratory features			
Site of lymphadenopathy	Any peripheral and/or internal site	Mainly cervical	Peripheral and/or internal
Size of lymph nodes	Variable, usually large and increasing	Variable, usually small, up to 2 cm	Variable, usually small, up to 2-3 cm
Systemic symptoms	Fever, night sweats, weight loss (B-symptoms) are common	Fever almost always, night sweats, flu-like symptoms	Fever common, other systemic features of SLE present
Haematological findings	Very variable (leukocytosis, thrombocytosis or cytopenias)	Leukopenia or low-normal counts	Leukopenia, lymphocytopenia, thrombocytopenia common
ANA or other autoantibodies	Rare (low titers)	Uncommon or low titers	Almost always in high titers
Histological features			
Necrosis	Coagulative necrosis (when present)	Usually prominent with karyorrhectic debris	Common, with karyorrhectic debris
Nodal architecture	Usually complete effacement	Usually partial effacement	Usually partial effacement
Polymorphous histiocytic infiltrates	Rare (CD68+, MPO -)	Prominent (CD68+, MPO +)	Prominent (CD68+, MPO +)
Neutrophils	Present	Absent	Present but rare
Plasmacytoid monocytes	Rare or Absent	Common	Common
Plasma cells	Scarce	Scarce	Numerous
Immunoblasts	Yes	Variable, may be atypical, T-phenotype	Variable
Hematoxylin bodies	Absent	Absent	Present
Azzopardi phenomenon	Absent	Absent	Present
Vasculitic lesions	Absent	Absent	Present
Immunophenotypic features	CD4+ >>CD8+ or CD4+CD8+ cells (abnormal T-cell phenotype)	CD8+ cell predominance	CD8+ cell predominance
Clonal T-cell receptor rearrangements	Yes	No	No

* encrustation of blood vessel walls with nuclear material due to fibrinoid necrosis