Kikuchi histiocytic necrotizing lymphadenitis: clinicopathological and immunohistochemical study

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خلاصة: تم بحث الملامح السريرية والمورفولوجية والكيميائية النسجية المناعية في عشر حالات مصابة بالشكل النسيجي للعُقد اللمفية من داء كيكوشي. وقد تم تشخيص اثنين من هؤلاء على أنهما حالتا ذئبة حمامية مجموعية. إن داء كيكوشي والذئبة الحمامية المجموعية لا يكاد يمكن تمييز أحدهما عن الآخر من الناحية المورفولوجية. ولم تكن الخلايا البلازمية، ولا ارتشاح العدلات، والأجسام الأليفة للهيماتوكسيلين والالتهاب الوعائي، مفيدة في التمييز بين الحالات. ولكن أمكن التمييز نسيجياً بين التهاب العُقد اللمفية الكيكوشي وبين الورم اللمفي الخبيث. وشملت الملامح المورفولوجية التي تستبعد الخباثة: الطبيعة المتعدّدة الأشكال للرُشاحة الخلوية، وعدم وجود انقسام خلوي تفتّلي غير طبيعي، والحفاظ على الشكل الجيباني في المناطق الفاصلة ووجود تمزُّق نووي داخل الخلايا وخارجها.

ABSTRACT Clinical, morphological and immunohistochemical features of 10 cases having the lymphnodal histological pattern of Kikuchi disease were examined. Two of these were diagnosed as systemic lupus erythematosus (SLE). Morphologically, Kikuchi disease and SLE were nearly indistinguishable. Plasma cells, neutrophilic infiltration, haematoxyphilic bodies and vasculitis were not useful in differentiating the conditions. Kikuchi lymphadenitis and malignant lymphoma however could be differentiated histologically. Morphological features that exclude malignancy included: polymorphous nature of cellular infiltrate, absence of abnormal mitosis, preservation of sinusoidal pattern in intervening areas and presence of extracellular and intracellular karyorrhectic debris.

La lymphadénite nécrosante histyocytaire (maladie de Kikuchi) : étude clinico-pathologique et immuno-histochimique

RESUME Les caractéristiques cliniques, morphologiques et immuno-histochimiques de 10 cas montrant l'aspect histologique ganglionnaire de la maladie de Kikuchi ont été examinées. Deux de ces cas avaient été diagnostiqués comme lupus érythémateux systémique. Sur le plan morphologique, il était quasiment impossible de faire la distinction entre la maladie de Kikuchi et le lupus érythémateux systémique. Les cellules plasmatiques, l'infiltration neutrophile, les corpuscules hématoxyliques et les vascularites n'étaient pas utiles pour faire la distinction entre les conditions. La lymphadénite de Kikuchi et le lymphome malin peuvent toutefois être différenciés sur le plan histologique. Les caractéristiques morphologiques qui excluent la malignité comprenaient : la nature polymorphe de l'infiltrat cellulaire, l'absence de mitose anormale, la préservation du caractère sinusoïdal dans les zones d'intervention et la présence de débris karyorrhectiques extra- et intracellulaires.

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Introduction

Histiocytic necrotizing lymphadenitis, or Kikuchi disease, is a benign, self-limiting condition that in some instances may be misinterpreted as malignant lymphoma [*1*]. It was first described in 1972 in Japan [*2*]. Additional reports subsequently appeared indicating the recognition of this disease in the United States of America [*3*], Germany [*4*], Sri Lanka [*5*], Greece [*6*], the United Kingdom [*7*], Hong Kong [*8*], Australia [*9*] and Belgium [*10*]. Reports of this disease from the Middle East are very few and include only 5 cases from Saudi Arabia [*11*] and 5 from Qatar [*12*].

The aim of our study was to review the clinical features, histological findings and immunophenotyping of the cellular population of cases of Kikuchi disease in the Region in order to facilitate recognition of the disease. Special emphasis was placed on the differentiation of Kikuchi disease from both malignant lymphoma and systemic lupus erythematosus (SLE) which are considered the most important differential diagnoses of this disease [*13,14*].

Methods

The study comprised 10 cases with apparent histological features of Kikuchi histiocytic necrotizing lymphadenitis. These cases were collected from the surgical pathology files of university hospitals in the United Arab Emirates, Bahrain and Iraq over a period of 8 years. Clinical features, including site of lymphadenopathy, symptoms and signs, and laboratory investigations, were obtained from the medical files of patients. The laboratory data required were blood count, erythrocyte sedimentation rate (ESR), serological tests [toxoplasma, Epstein-Barr virus (EBV), cytomegalovirus (CMV) and human immunodeficiency virus (HIV)], blood culture and autoimmune studies (antinuclear antibodies, lupus erythematosus preps and anti-DNA antibodies). These investigations confirmed the diagnosis of SLE in 2 of the 10 cases that had previously been diagnosed with Kikuchi necrotizing lymphadenitis on histological grounds. These 2 cases were included in the study to compare the morphological features of their lymph node biopsies with the other 8 cases of confirmed Kikuchi disease.

Pathology records were reviewed to obtain the gross features of the lymph nodes. Multiple haematoxylin and eosin-stained sections prepared from paraffin-embedded lymph nodes were examined for the following changes: effacement of the nodal architecture, necrosis, karyorrhexis, type and degree of cellular infiltrate around necrotic areas and elsewhere in the lymph node, mitosis, follicular hyperplasia, paracortical hyperplasia, and pericapsular inflammation. Each of these findings was graded semi-quantitatively as absent (–), mild (+), moderate (++) or marked (+++). Effacement of the nodal architecture was graded as absent (–), focal (+), partial (++) or total effacement (+++). Special stains, including Giemsa, periodic acid-Schiff (PAS), reticulin, Ziehl–Neelsen for acid-fast bacilli and Grocott stain for fungi, were performed.

Formalin-fixed, paraffin-embedded tissue sections were used for immunohistochemical studies by avidin–biotin–peroxidase complex method (Vectastain, ABC kit, Vecta Laboratories, California, United States of America). The antibodies used were lysozymes and alpha 1antitrypsin for histiocytes, CD3 for T-cells, CD20 for B-cells and CD35 for dendritic reticulum cells and HLA-DR (all were purchased from DAKO).

Results

Clinical features

Clinical features of the 10 cases are given in Table 1. There were 8 females and 2 males (F:M = 4:1). The mean age was 27 years (range 14–35 years). All presented with enlarged cervical lymph nodes and were clinically diagnosed as either tuberculous lymphadenitis or lymphoma. Associated axillary nodal enlargement was detected in 2 patients. The mean duration of the disease on presentation was 26.3 days (range 20–35 days). Fever was observed in half of the patients and pain in 5 patients. Weight loss occurred in 6 patients. No patient presented with skin lesion or enlarged liver or spleen. The lymphadenopathy disappeared within a mean period of 46 days (range 30–60 days) without treatment. The 2 patients who proved serologically to have SLE were females aged 35 years and 41 years. They presented with painless isolated cervical lymphadenopathy of 1 month duration. This was associated with fever and polyarthralgia but no weight loss, skin lesions or hepatosplenomegaly.

Laboratory findings

Elevation of ESR was present in all cases with a mean of 32 mm/hour (range 25–107 mm/hour). All patients had normal blood count except leukopenia with relative lymphocytosis in 2 patients. All serological tests were negative. Two patients were diagnosed with SLE because of the results of autoimmune studies.

Pathological findings

The lymph nodes examined had an average greatest dimension of 1.5 cm (range 1.2–2.0 cm). They were firm in consistency

Table 1 **Clinical and serological data of the 10 cases**

Clinical and serological features	Present No.	Present %
Enlarged cervical lymph nodes	10	100
Enlarged axillary lymph nodes	2	20
Fever	6	60
Pain	5	50
Weight loss	6	60
Skin rash	0	0
Splenomegaly	1	10
Hepatomegaly	1	10
High erythrocyte sedimentation rate	10	100
Leukopenia	2	20
Lymphocytosis	2	20
Autoantibodies	2	20

Table 2 **Histopathological data of the 10 cases**

Histopathological features	Present No.	Present %
Pathological areas		
Loss of nodal architecture		
Partial	5	50
Complete	5	50
Necrosis	6	60
Haematoxylin bodies	0	0
Karyorrhexis	10	100
Mantle of histiocytes	10	100
Lymphocytes	10	100
Plasma cells	10	100
Atypical mononuclear cells	2	20
Polymorphs	2	20
Intervening areas		
Follicular hyperplasia	4	40
Paracortical hyperplasia	10	100

Figure 1 **Central area of necrosis containing karyorrhetic nuclear and cellular debris (H&E × 200).**

Figure 2 **A cellular zone bordering the area of necrosis (lower right) consisting of large histiocytes with eosinophilic or clear cytoplasm (H&E × 250).**

Figure 3 **One of the cases of Kikuchi lymphadenitis showing cellular infiltrate formed of atypical cells with large irregular nuclei, coarse chromatin and mitosis (H&E × 400).**

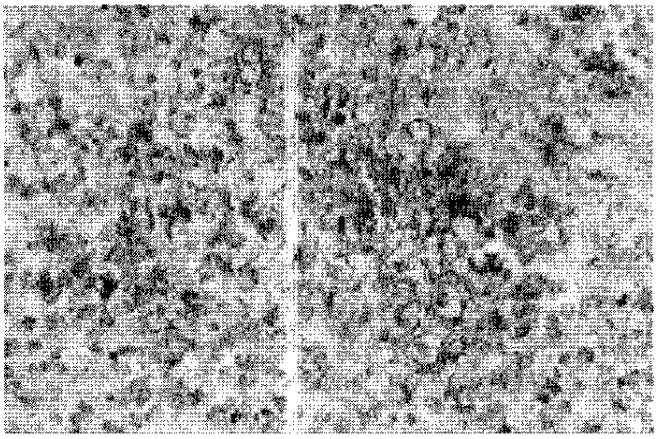

Figure 5 **Positive immunostaining of the histiocytes (shown in Figure 2) for alpha 1-antitrypsin which appeared as granular cytoplasmic staining (avidin-biotin–peroxidase complex method × 250).**

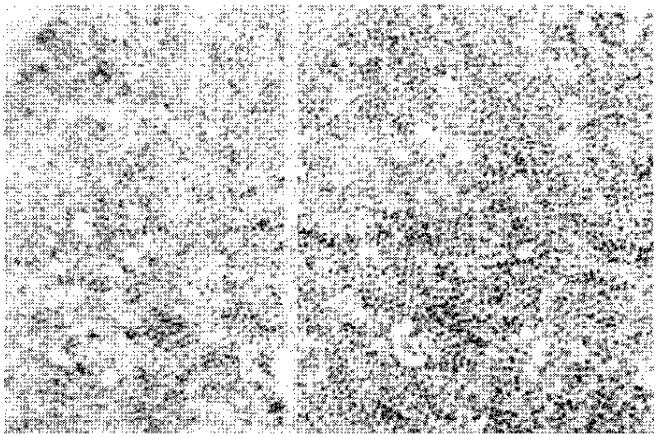

Figure 4 **The intervening areas showing some histiocytic cells scattered among the lymphoid population giving a starry sky appearance (H&E × 100).**

with tan-coloured cut section. Grossly apparent yellowish foci of necrosis were evident in only one case.

The morphological data of the 8 cases of Kikuchi lymphadenitis and the 2 cases of SLE are shown in Table 2. All 8 cases of Kikuchi disease revealed either partial (4 cases) or complete effacement of the lymph nodal architecture (4 cases). Well-circumscribed areas of necrosis were seen in 6 cases; the remaining 2 cases showed no overt tissue necrosis. The necrotic areas involved cortical, paracortical and medullary sites. They appeared as either multiple small necrotic foci (2 cases) or confluent patches (4 cases). Necrotic areas consisted of eosinophilic structureless material and contained a variable amount of basophilic karyorrhetic nuclear and cellular debris with some fragmented cells (Figure 1). The necrotic areas were surrounded by a cellular zone of variable thickness consisting mainly of histiocytes which appeared large, round-to-oval with eosinophilic or clear cy-

Table 3 **Immunohistochemical data of the 10 cases**

Immunohistochemical features	Present	
	No.	%
Histiocytes	10	100
HLA-DR+	10	100
T-cells (CD3+)	10	100
B-cells (CD20+)	0	0
Dendritic cells (CD35+)	0	0

toplasm that sometimes contained basophilic nuclear debris. The nuclei were round or irregular in shape and central or eccentric in position. These cells were localized, mainly bordering the areas of necrosis (Figure 2).

Scattered among the histiocytes was karyorrhetic debris. The peripheral part of the cellular zone consisted of a mixed cell population with the predominating cells larger than small lymphocytes. They had round nuclei with or without prominent nucleoli. Pale eosinophilic cytoplasm was observed. Such cellular features corresponded to the so-called plasmacytoid monocytes. Other cellular elements included small mature lymphocytes and immunoblasts. In 2 cases, the cellular infiltrate around the necrotic areas showed some atypical mononuclear cells which had large irregular nuclei, coarse chromatin pattern and some mitotic figures, thus resembling malignant lymphoma (Figure 3), although abnormal mitosis was never seen. Plasma cells were usually scant and polymorphonuclear cells were absent. The 2 cases with no overt necrosis showed clusters and sheets of histiocytes which were located mainly in the cortical and paracortical areas and appeared weakly basophilic on Giemsa stain. The histiocytic cells were interspersed with few plasmacytoid cells and immunoblasts. No bacteria, mycobacteria or fungi were seen in any case.

Follicular hyperplasia was found in 2 of the 8 cases of Kikuchi disease. In the remaining 6 cases, lymphoid follicles were either normal or absent due to effacement of the nodal architecture. Paracortex showed mild to moderate widening with some histiocytic cells scattered among the lymphoid population giving a "starry sky" appearance (Figure 4). Capsular and pericapsular lymphocytic infiltration was present in all cases. The uninvolved areas showed preservation of the subcapsular and medullary sinuses.

The nodal architecture of the 2 SLE cases was partially effaced in one case and completely effaced in the other. Necrosis was minimal in both cases. The pathological areas appeared as multiple foci of histiocytic infiltrate that was admixed with karyorrhetic debris, immunoblasts and mature lymphocytes. The morphology of these cells was similar to that described in the cases of Kikuchi disease. Plasma cells were scant. Both cases showed follicular and paracortical hyperplasia. Sinus histiocytosis was seen in only one case and haematoxyphilic bodies were not seen in either case.

Immunohistochemical data are given in Table 3.The histiocytic cells around necrosis revealed positive immunostaining for lysozyme (Figure 5) and alpha 1-antitrypsin to a similar degree and pattern which appeared as cytoplasmic granular staining. The mixed cells adjacent to the histiocytic cells were mostly HLA-DR+, immunoblasts and small lymphocytes; a few of the so-called plasmacytoid monocytes were CD3+ (T-cells). On the other hand, B lymphocytes (CD20+) and dendritic cells (CD35+) were consistently absent in the diseased areas.

Discussion

The clinical and histological features of the 8 cases with Kikuchi necrotizing lymphadenitis were generally in accord with several of the reported characteristics of this disease [*1,7,10–12,14–16*]. However, certain clinicopathological points need to be stressed.

First, the necrotizing process was initially described by Kikuchi to be localized to the cortical and paracortical areas [*17*]. This was later confirmed by Feller et al. [*18*]. Nevertheless, we found that the necrotic areas involved not only the cortex and paracortex but also extended to the medullary areas. Similar observations have been reported by Unger et al. [*16*] and Dorfman and Berry [*1*].

Second, the absence of overt tissue necrosis in 2 cases concurs with studies in which tissue necrosis was not found in some cases [*1,8,13,14*]. Therefore, overt necrosis should not be considered an important diagnostic criterion for this disease and the term "necrotizing lymphadenitis" may be misleading. This term has been criticized previously by other investigators such as Woodruff [*19*] and Chamulak et al. [*13*].

Third, the so-called plasmacytoid cells constituted an important element of the cellular infiltrate in the cases presented in our study. The immunophenotype of these cells has been challenged by many investigators. Some investigators have reported positivity of these cells to T-cell markers and called them plasmacytoid T-cells [*4,15,18*]. On the other hand, Facchetti et al. revealed the monocytic origin of these cells and demonstrated the presence of molecules related to alpha, beta and gamma chains of HLA-DR on these cells [*10,20*]. The term plasmacytoid monocytes was therefore proposed. Another confusing report was that of Chamulak et al. who failed to demonstrate staining of the plasmacytoid cells with any of the cell markers used [*13*]. Chamulak et al. believed that these cells were a specific type of monocyte. In our study, most of the so-called plasmacytoid cells expressed HLA-DR antigen while only few were phenotypically T-cells. This finding agrees with Facchetti et al., who claimed that an interaction between HLA-DR positive antigen proces-sing and presenting cells and plasmacytoid monocytes can result in the recruitment and proliferation of T lymphocytes with the generation of cytotoxic T-cells [*10*]. Nonetheless, it should be stressed that all immunological marker studies, including our own, have been performed on only a few cases. Such studies should be applied to much larger series for better understanding of the immunobiology of Kikuchi disease. Irrespective of the nature of these plasmacytoid cells, we support the view of Chamulak et al. who objected to the use of the word "plasmacytoid" because these cells have no histological resemblance to plasma cells and accordingly they might be misidentified [*13*].

There is much controversy about the etiology of Kikuchi lymphadenitis. All serological tests in our study were negative. The same results have been obtained by other researchers [*7,9,21*]. Kikuchi [*22*] however reported elevated titres for toxoplasma in some of his earlier cases, while Feller et al. [*18*] reported elevated titres for *Yersinia* species in all 3 patients included in their study. Rivano et al. also reported elevated titres for *Yersinia* species in 2 of 8 studied cases [*15*]. A viral etiology has been suspected because of associated clinical findings, such as upper respiratory prodrome, lymphocytosis and lack of response to antibiotics, and histological findings, such as paracortical hyperplasia, proli-

feration of immunoblasts and predominance of T lymphocytes [*16*]. Similar findings were observed in our study and in others [*1,13–15*].

Although Kikuchi disease is a rare, self-limiting condition, its recognition is very important to avoid the erroneous diagnosis of lymphoma as happened initially in 40% of the cases reported by Turner et al. [*21*] and in a high percentage of the 100 cases reported by Dorfman [*23*]. The diagnosis of lymphoma was also seriously considered in all 10 cases described by Chamulak et al. [*13*]. In our view, the features most likely to cause misdiagnosis of necrotizing histiocytic lymphadenitis as lymphoma include: effacement of the nodal architecture which might be partial or complete; presence of atypical features in some of the infiltrating cells, such as nuclear irregularity, dense chromatin pattern and possibly mitotic figures; obliteration of the sinusoidal pattern in the pathological areas; and presence of starry sky appearance in the intervening areas.

Nevertheless, careful examination of multiple tissue sections should reveal some histological features that will help the pathologist to exclude malignancy. There are four primary histological features that exclude malignancy. First, the cellular infiltrate has a polymorphous nature. Second, mitotic figures are usually far fewer than in lymphoma and atypical mitosis is never seen. Third, the sinusoidal pattern in the intervening areas is preserved. Fourth, karyorrhetic debris is extracellular and intracellular; this contrasts with lymphoma in which karyorrhexis, if present, is usually intracellular only. The histological diagnosis of Kikuchi disease in our 8 cases was verified by their benign course, since all patients showed spontaneous resolution of adenopathy within 30–60 days. It is also worth noting that flow cytometry can be a useful tool for differentiation between Kikuchi lymphadenitis and lymphoma, since DNA content in the former is usually diploid [*24*].

SLE is another important differential diagnosis of Kikuchi disease. The histological differentiation between the two conditions is very difficult or almost impossible as seen with the 2 cases in our study and the 2 cases included in the study of Dorfman and Berry [*1*]. Turner et al. [*21*] and Dorfman [*23*] suggested that plasma cells may be prominent in association with SLE, whereas these cells are usually absent or sparse in Kikuchi disease. However, in the SLE cases of Dorfman and Berry [*1*], as well as in our own, plasma cells were very few. Haematoxyphilic bodies, which are regarded as a diagnostic feature of SLE [*24*], were not seen in our cases nor in the cases of Dorfman and Berry [*1*]. Although Tsang et al. [*14*] reported that SLE may be differentiated histologically from Kikuchi disease by the presence of neutrophilic infiltration, our study and that of Dorfman and Berry [*1*] noted a lack of granulocytes in the lymph nodes of patients with either Kikuchi or SLE. Ali and Horton [*7*] reported that in SLE there may be vasculitis, although this feature is rare [*25*]. Thus, the morphological features of lymph nodes in SLE may be indistinguishable from those of Kikuchi disease.

It is of further interest that both conditions predominantly affect young women. Patients with Kikuchi disease might present with SLE-like clinical features [*1*]. Moreover, electron microscopy has demonstrated tubuloreticular structures in the cytoplasm of lymphocytes and histiocytes in patients with Kikuchi similar to those seen in SLE [*26*]. Accordingly, we support the assumption of Imamura et al. [*27*] and Felgar et al. [*28*] that Kikuchi disease may reflect a self-limiting SLE-like autoimmune

condition. On the other hand, we believe that differentiation between the two conditions should depend upon serological autoimmune studies and not on lymph node histology alone. This has been also emphasized by Tsang and Chan [*29*].

In conclusion, Kikuchi disease is a benign, self-limiting condition which commonly affects cervical lymph nodes of young women. Morphologically, it is characterized by a cellular infiltrate formed mainly of histiocytes and lymphocytes of the T-cell phenotype. Although necrosis is not a constant feature, karyorrhexis is an important characteristic that is always present. The disease can be differentiated from malignant lymphoma by careful attention to and awareness of its morphological picture, even though it cannot be histologically distinguished from SLE in most instances. Therefore, serological tests should always be recommended in such cases to exclude SLE.

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