Histiocytic Necrotizing Lymphadenitis (Kikuchi's Disease): Clinicopathologic Characteristics of 23 Cases and Literature Review

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Abstract

Kikuchi's disease or histiocytic necrotizing lymphadenitis is a self limiting disorder which usually affects young women and manifests clinically by cervical lymphadenopathy with or without fever. Though the disease has been described since 1972, many clinicians and pathologists are unaware of its existence. We therefore reviewed 23 cases of Kikuchi's disease in Songklanagarind Hospital from 1987 to 1996. Clinical data, histopathology including immunostaining were presented together with brief literature review. We found 18 women and 5 men with the age range 9-57 years. The sites of nodal enlargement were cervical in 17, axillary in 3 and unknown in 3 cases. Typical histologic features namely patchy paracortical lymphohistiocytic aggregates with variable karyorrhexis and absence of granulocytic infiltration were seen. Immunostaining confirmed that the principle cells were histiocytes and T-lymphocytes. Importance in the recognition of the entity was emphasized for it may be mistaken for other infective lymphadenitis or lymphoma.

Key word : Lymphadenitis, Necrotizing Lymphadenitis, Clinicopathologic Characteristics, Literature Review

Histiocytic necrotizing lymphadenitis or Kikuchi's disease is a self-limiting cause of lymphadenopathy, first described in Japan by Kikuchi et al in 1972[1]. Fujimoto et al, later in the same year, independently described the entity[2]. So that it is sometimes called Kikuchi-Fujimoto disease[3]. The disease is more prevalent in Asian countries[4-6] though small series were also reported from other parts of the world[7,8].

The disease usually presents with cervical lymphadenopathy with or without fever in young adult women[9]. Persistence of nodal enlargement for a few weeks to months and unresponse to antibiotic treatment lead to the biopsy of the node to

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rule out malignancy. The diagnosis is made by routine histologic examination characterized by paracortical necrotizing lymphohistiocytic foci without granulocytic infiltration. The disease is now well documented, however, the etiology is still unknown.

Though the disease has increasingly been reported, many clinicians and pathologists seem to be unaware of its existence. Recognition of the entity is important for misdiagnosis to lymphoma will result in inappropriate and harmful treatment. We therefore reviewed cases of Kikuchi's disease in Songklanagarind Hospital of 10 years' experience. Clinical data, histopathology and immunostaining of 23 cases are presented together with a review of the literature.

MATERIAL AND METHOD

Case selection

The cases in this study were obtained from the files of the Anatomical Pathology Unit of the Department of Pathology, Songklanagarind Hospital. Cases recorded from January 1987 to December 1996 were included. The cases coded as Kikuchi's disease/lymphadenitis were retrieved. In addition, cases that may have been misdiagnosed as other types of lymphadenitis were included, cases signed with an ending term of lymphadenitis excluding caseous or tuberculous lymphadenitis were also listed out. All cases obtained by both searching strategies were reviewed microscopically by the authors to select the cases of Kikuchi's disease. A total of ten cases readily signed as Kikuchi's disease and thirteen cases not previously signed as Kikuchi's disease were found and included in the study. All the latter thirteen cases were cases before 1991 and were previously signed as necrotizing lymphadenitis of unknown cause.

Histopathology and Immunohistochemical Studies

Histologic features were evaluated on paraffin sections of formalin-fixed lymph node tissue stained with hematoxylin and eosin. Acid fast and Gomori methenamine silver (GMS) stains were also done for all cases to rule out possible organisms. Immunohistochemical staining was performed on paraffin sections of all cases by use of conventional avidin-biotin complex method. Primary antibodies employed were CD45RO (a marker for T-cell), L26/CD20 (a marker for B cell) and CD68 (a marker for histiocyte).

Table 1. Summarization of 23 cases.

Female : Male		18 : 5
Age	range (yr)	9-57
	mean (yr)	28
	median (yr)	30
Site of lymph node		
	cervical	17
	axilla	3
	unknown	3
Presenting symptom		
	palpable adenopathy	22
	FUO*	1
Duration of symptom		
	range (wk)	0.78 -16
	median (wk)	3
Fever		2/13
Leukopenia		3/4

* FUO, fever of unknown origin

RESULTS

Clinical data

The clinical features of 23 cases are summarized in Table 1. Most of the cases were between 20-40 years of age (Fig. 1). All cases except one were less than 40 years old. The disease was more prevalent in women with a female to male ratio of 3.6:1. All of the patients presented with nonpainful palpable lymph node except one. This case presented with a 2-week fever of unknown origin and was admitted for evaluation. Cervical lymphadenopathy was just found during admission. One case had an accompanying sore throat. Fever was noted in 2 out of 13 cases, where in the remaining 10 cases it was not stated.

The lymph node enlargement was limited to right cervical in 7, left cervical in 8, bilateral cervical in 2, axilla in 3, and not stated in 3 cases. Duration of symptoms ranged from 2 days to 4 months with the median of 3 weeks. Antibiotic treatment was given in 9 cases and open biopsies were performed after unresponse to antibiotics.

Laboratory investigation was done in only a few cases. Leukopenia with a white blood cell count fewer than 4,000/mm^3 was found in 3 of 4 patients examined. The remaining one case had mild leukocytosis. In the admitted case, serologic tests for various infective agents were done. These included tests for leptospirosis, scrub typhus, murine typhus, VDRL and EBV, and all were not remarkable.

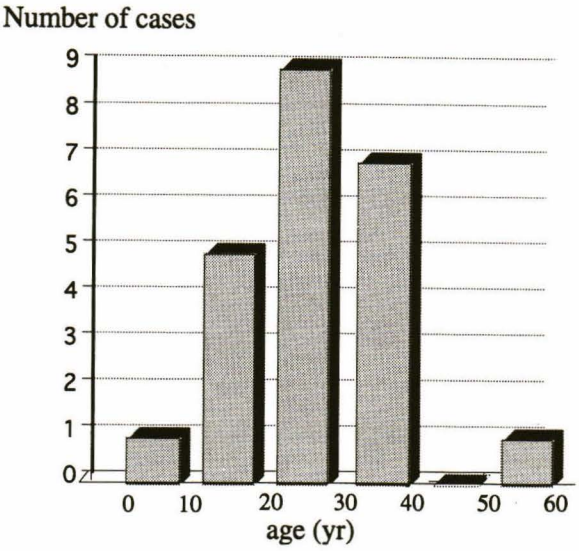

Fig. 1. Age distribution of the patients.

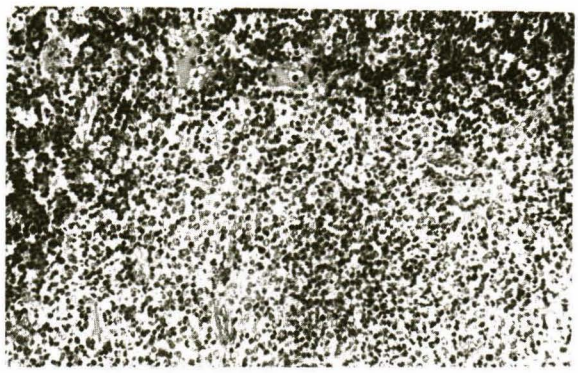

Fig. 3. Medium power view showing lymphohistiocytic aggregates with karyorrhectic debris. H&E, x 200.

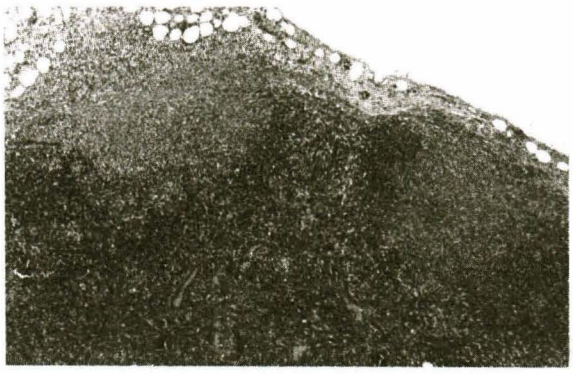

Fig. 2. Low power view of the involved node revealed pale staining cortical foci. Capsular extension to perinodal fat was noted. Hematoxylin and eosin, x 40.

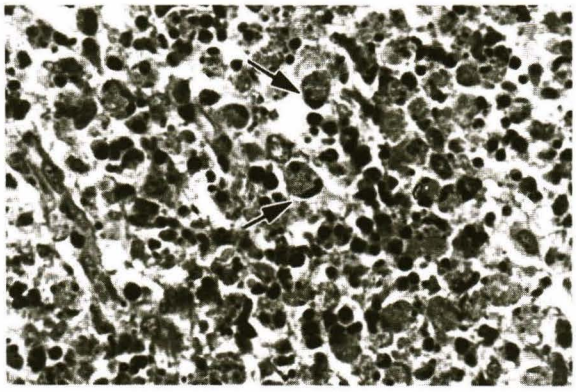

Fig. 4. High power view showing extensive karyorrhexis and prominent phagocytic histiocytes with crescentic nuclei (arrow). H&E, x 400.

Follow-up information was limited. Most of the patients returned to the hospital within the first two weeks for the purpose of evaluation of the biopsy wound only.

Microscopic findings

Histologic features characteristic of Kikuchi's disease that have been described in the literature were observed. Patchy pale staining foci in paracortex were evident in the low magnification (Fig. 2). The areas were either discrete and fairly well-defined or irregular in shape and confluent. All cases had more than one foci, mainly located interfollicularly in the cortex or subcapsular. The subcapsular foci were usually associated with various degrees of capsular fibrosis and pericapsular lymphohistiocytic infiltration.

The cellular components of the foci were a mixture of histiocytes, small and transformed lymphocytes including immunoblasts and scattered karyorrhectic nuclear debris (Fig. 3). The histiocytes which accounted for 60-80 per cent of the population cells had various features including 1) phagocytic histiocytes with eccentrically placed

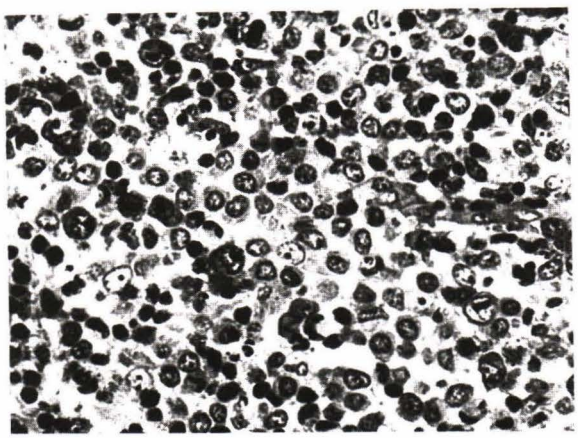

Fig. 5. High power view showing prominent plasmacytoid monocytes. H&E, x 400.

crescentric nuclei and voluminous cytoplasm containing debris (the so-called "crescentic" histiocyte) (Fig. 4). Some of these histiocytes with crescentic nuclei were non-phagocytic; 2) non-phagocytic histiocytes with vesicular centrally placed nuclei and pale pink cytoplasm ; 3) the so-called "plasmacytoid" monocytes which were medium sized cells with eccentrically placed round nuclei and amphophilic cytoplasm (Fig. 5); and 4) histiocytes with foamy cytoplasm. Foamy histiocytes were the most rarely seen whereas the others were mixed. Phagocytic crescentic histiocytes were prominent when karyorrhexis was marked. Prominent foamy histiocytes were found only in one case.

Scattered karyorrhectic nuclear debris were present in all foci in variable number. The necrotizing cells showed typical apoptotic changes, including cell shrinkage, chromatin condensation, eosinophilic cytoplasm, and formation of apoptotic bodies, observed as karyorrhetic debris. Granulocytic infiltration was absent. In two cases, karyorrhexis was marked and appeared as abscess formation. Obvious coagulative necrosis, usually associated with thrombosed vessels, was observed in 6 cases. Small lymphocytes, transformed lymphocytes with irregular nuclei and immunoblasts were variable in number ranging from 20-40 per cent of the cells.

The paracortex outside the lesion were hyperplastic appearing as starry-sky or mottling appearance in nearly all cases. The follicles showed marked reactive hyperplasia in 2 cases, some degree of hyperplasia in 4 cases and were unremarkable in the remainder. Both acid fast and GMS stains revealed negative results.

Immunohistochemical studies

Most cells in the involved foci were positively stained with CD68. These cells included both phagocytic and nonphagocytic histiocytes and plasmacytoid monocytes. The lymphocytes in the foci either small and larger tranformed lymphocytes were positively stained with T-cell marker (CD45RO). Strikingly, membrane staining with CD45RO was prominently observed in both phagocytosed and non-phagocytosed necrotic cells. CD20 positive cells were rare in the foci.

DISCUSSION

Though this entity was first recognized in Japan in 1972 and apparent in the English literature since 1977[10], the disease seems to be unknown to our society either to clinicians or pathologists. As in our case, the disease was not diagnosed until 1991. To our knowledge, there has been no publication of this entity in Thailand so far. Only a case of a Thai woman was cited to have been reported in Finland[8].

The clinical features of the present series are almost similar to those reported in the literature. Our findings confirm that Kikuchi's disease is a benign, self-limited lymphadenopathy, primarily affects cervical lymph nodes in young adults. Women are generally reported to be more commonly affected than men with the ratio of female to male 1.5-4 : 1[5,7,9]. Female predilection was also evident in our series with the ratio of 3.6:1. The reason for the female preponderance is not known. Though the disease was reported with a wide age range from the first to the seventh decade of life, most of the patients were between 20-40 years.

The most frequent presenting symptom is painful or painless persistent cervical lymphadenopathy that does not respond to antibiotics. The far less common sites of involvement are axillary, supraclavicular and retroperitoneal lymph nodes. Generalized lymphadenopathy is rare[3,11,12]. Other associated symptoms include fever, fatigue, malaise, myalgia and sore throat. The disease usually presents with fever of unknown origin and needs hospitalization for evaluation as in one case in our series[11,12]. The disease runs a benign course and lymphadenopathy resolves spontaneously within a

few weeks or months[9]. A small number of patients might experience a recurrent attack[3]. However, many clinical and laboratory data including fever, complete blood count and follow-up data were incomplete in the present study. Leukopenia that was reported in 25-60 per cent of the cases, could not be evaluated in our series.

The histopathologic features are not different from other series. The principle features are paracortical aggregation of lymphohistiocytic cells with variable degree of karyorrhexis in the absence of neutrophils[5,6,13]. Kuo TT who recently reported clinicopathologic features of 75 cases has proposed three histologic subtypes as proliferative, necrotizing and xanthomatous types[6]. Necrotizing type was defined when any degree of coagulative necrosis was evident. The author found the necrotizing type to be the most common type accounting for half of the cases followed by 29.1 per cent of proliferative types and 17.7 per cent of xanthomatous type. In addition, he compared the clinical features among the three types and found some correlation. Our series is somewhat different in the proportion of the subtypes. Only one forth of the cases showed definite coagulative necrosis and none could be classified as xanthomatous type, only prominent xanthomatous reaction surrounding coagulative necrotic foci was seen in one case. We thought that the difference resulted from the subjective criteria on the designation of coagulative necrosis. The overlapping and confusion can occur in the microscopic appearance between extensive karyorrhexis and coagulative necrosis. The proposed histological subtypes, therefore, need some clarification. The usefulness of the classification, in addition, is not clear.

Recent evidence has supported that apoptotic cell death is a mechanism of cellular destruction in this entity and that apoptosis in the disease is mediated by cytolytic lymphocytes[14,15]. In addition to the characteristic light microscopic appearance of karyorrhectic debris that supports apoptotic cell death, PCR-based technique to detect apoptotic cell in paraffin section has been developed[16] and was applied to comfirm apoptotic cell death in the lesion of Kikuchi's disease[14,15]. The authors, in addition investigated the mechanism of the apoptosis. By the demonstration of cell -specific cytolytic protein essential for provoking apoptosis in the apoptotic bodies and in the infiltrating lymphocytes which are mostly CD8+ T cells, comes to the suggestion that apoptosis is probably being mediated by cytolytic lymphocytes and that cytolytic lymphocytes themselves are undergoing apoptosis. Apoptosis mediated by cytolytic T-lymphocytes is known to be a method by which host cells abort viral replication. This information is therefore indirect evidence that viral infection may play a role in the etiology of the disease.

The definite etiology of Kikuchi's disease is still unclear. The association of the disease with several infectious agents has been investigated. These agents include Epstien-Barr virus[17,18], cytomegalovirus, varicella-zoster virus, herpesvirus-6[19], HIV[20], Parvovirus B19[21], Yersinia-enterocolitica[22] and toxoplasma[10]. However, no convincing causal relation has been found. Possible autoimmune mechanism is also proposed for there are some reported cases that Kikuchi's lymphadenitis developed in association with Still's disease, systemic lupus erythrematosus and mixed connective tissue disease[22,23,24].

Recognition of this entity is important. Clinically, Kikuchi's disease should be considered in the differential diagnosis of cervical lymphadenopathy of unknown etiology particulary in young adult women. The disease can be diagnosed by routine histologic examination without any other special stain. However, if the pathologist is not familiar with this entity, it can be mistaken for other infective lymphadenitis or lymphoma, especially when karyorrhexis is minimal[9,25]. This may result in inappropriate or unnecessary treatment. As in our case, it was mistaken for acute necrotizing lymphadenitis before 1991. In such cases, a patient may be prescribed unnecessary antibiotics. Either clinicians or pathologists, therefore, should know the existence and nature of this specific clinicopathologic entity, so that correct diagnosis can be made and unnecessary treatment can be avoided.

SUMMARY

Clinical and histologic features of the present series of Kikuchi's disease which included the 23 cases in Songklanagarind Hospital are correlated with those reported in the literature. The disease manifested clinically with acute or subacute cervical lymphadenopathy with propensity in young women. An exception of one case presented with fever of unknown origin. Characteristic patchy para-

cortical lymphohistiocytic aggregates with a variable degree of karyorrhexis and absence of granulocytic infiltration were seen. Various cellular features of the infiltrating histiocytes were emphasized including the so-called crescentric histiocytes and plasmacytoid monocytes. Immunostaining confirmed that histiocyte and T-lymphocytes are the principle cells of the lesion. From the literature review, recent evidence has shown that cytolytic-mediated apoptosis is the mechanism of cell destruction, so that viral infection is thought to play a role in the etiology of the disease. Importance in the recognition of this entity is emphasized because being mistaken for other disease especially lymphoma would result in inappropriate or harmful treatment.

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ฮิสติโอซัยติค นีโครไทซิง ลิมฟ์อาดีไนติส (โรคคิคูชิ) : ลักษณะทางคลินิกพยาธิวิทยาในผู้ป่วย 23 ราย และวารสารปริทัศน์

ปารมี ทองสุกใส, พ.บ., คณิตา กายะสุต, พ.บ.**

Kikuchi's disease หรือ histiocytic necrotizing lymphadenitis เป็นโรคที่หายได้เอง มักเป็นในผู้หญิงอายุน้อย และมาด้วยอาการต่อมน้ำเหลืองโตร่วมกับมีหรือไม่มีไข้ ถึงแม้โรคนี้จะมีรายงานครั้งแรกตั้งแต่ปี พ.ศ. 2515 แต่แพทย์ทางคลินิก และพยาธิแพทย์จำนวนมาก ยังไม่รู้จักโรคนี้ ดังนั้นผู้เขียนจึงรวบรวมผู้ป่วยโรคนี้ในโรงพยาบาลสงขลานครินทร์ ตั้งแต่ปี พ.ศ. 2530-2539 แล้วรายงานข้อมูลทางคลินิก จุลพยาธิวิทยา รวมทั้งผลการย้อมทางอิมมูโนวิทยา พบผู้ป่วยทั้งสิ้นจำนวน 23 ราย เป็นผู้หญิง 18 ราย ผู้ชาย 5 ราย มีอายุตั้งแต่ 9-57 ปี ตำแหน่งต่อมน้ำเหลืองพบมากที่สุดที่คอ 17 ราย รักแร้ 3 ราย และไม่ทราบตำแหน่ง 3 ราย ลักษณะทางจุลพยาธิวิทยาเป็นหย่อมการรวมกลุ่มของเซลล์ lymphocyte และ histiocyte และมีการแตกสลายของเซลล์ (karyorrhexis) โดยไม่พบเซลล์ neutrophil การย้อมทางอิมมูโนเคมี ยืนยันว่าเซลล์ในรอยโรคเป็น T-lymphocyte และ histiocyte โรคนี้มีความสำคัญเนื่องจากอาจวินิจฉัยผิดว่าเป็นต่อมน้ำเหลืองอักเสบจากการติดเชื้อ หรือเป็นมะเร็งต่อมน้ำเหลือง

คำสำคัญ : ต่อมน้ำเหลืองอักเสบ, นีโครไทซิง ลิมฟ์อาดีไนติส, ลักษณะทางคลินิกพยาธิวิทยา, วารสารปริทัศน์

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