

Fine Needle Aspiration Cytology of Kikuchi's Lymphadenitis: with Emphasis on Differential Diagnosis with Tuberculosis

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Background: Although Kikuchi's lymphadenitis (KL) has been known to have characteristic cytological features, pathologists encounter difficulties in making a diagnosis with fine needle aspiration cytology (FNAC). The objective of this study was to assess the diagnostic pitfalls of KL with FNAC, particularly with emphasis on differential diagnosis with tuberculosis. **Methods:** FNAC of 10 patients with a histological diagnosis of KL and tuberculosis was reviewed. **Results:** Acidophilic cells were observed in all the 10 KL cases, even if the smears were insufficient. Crescentic histiocytes were seen in 8, granular background in 7, and karyorrhectic debris in 3 cases. Epithelioid histiocytes or neutrophils were not seen in any of the KL cases. Of the 10 cases of tuberculosis, acidophilic cells were observed in 6 cases, crescentic histiocytes in none of them, cheese-like background in 9, karyorrhectic debris in 8, epithelioid histiocytes in 4, and neutrophils in 8 cases. **Conclusions:** The acidophilic cell could be the most sensitive but not the specific marker of KL with FNAC. The crescentic histiocytes might be the sensitive and considerably specific marker of KL. The cytological features distinguishing tuberculosis from KL may be cheese-like necrosis admixed with neutrophils and epithelioid histiocytes.

Key Words: Histiocytic necrotizing lymphadenitis; Cytology; Biopsy, Fine needle; Tuberculosis

Kikuchi's lymphadenitis (KL), also called as histiocytic necrotizing lymphadenitis, is a reactive condition of a lymph node which has a distinct clinical manifestation but unknown etiology.¹⁻³ In most of the cases, it presents as a cervical lymphadenopathy mainly in young adults, especially women.⁴ It undergoes a self-limiting course within a few weeks to several months. However, unnecessary excisional biopsy is still being performed in patients due to high occurrence of false negative or false positive rates of cytologic diagnosis based on fine needle aspiration cytology (FNAC).^{5,6} Although KL has been known to have characteristic cytological features such as, karyorrhectic debris, crescentic histiocytes, extracellular and intracellular apoptotic bodies, plasmacytoid lymphocytes and rare neutrophils, pathologists sometimes face difficulties in making a cytologic diagnosis because KL shares several cytologic features with other reactive and neoplastic conditions such as, tuberculosis, lupus lymphadenitis, malignant lymphoma, and nonspecific reactive lymphadenitis, etc.⁵⁻¹¹ In particular, KL shares many cytological and histological features with tuberculosis with extensive necrosis, and sometimes it is difficult to differentiate them cytologically.^{6,12} There have been several reports^{5-11,13,14} about FNAC of KL, however, the collective studies using cases confirmed by

histology have been not many. The objective of this study was to assess the diagnostic pitfalls of KL with FNAC, particularly with emphasis on differential diagnosis with tuberculosis.

MATERIALS AND METHODS

Cases of KL were obtained by examination of computer records covering the past 10 years from the Dankook University Hospital Pathology Database. We selected 10 cases, in which the patients had undergone FNAC as well as subsequent lymph node excision. Smears were wet-fixed with alcohol and stained with a modified Papanicolaou method and hematoxylin and eosin. Smears were carefully reviewed with focus on the cellularity, karyorrhectic debris, background material, crescentic histiocytes, and acidophilic cells.

For comparison with tuberculosis, 10 FNAC cases in patients whose lymph node revealed a histology of tuberculosis with extensive necrosis were selected in a similar manner from the same database, and they were reviewed as described above.

RESULTS

The clinical features of patients with KL are summarized in Table 1. The male to female ratio was 1 : 1, and their ages ranged from 9 to 29 years (mean, 20.4 years). The affected lymph nodes were all cervical lymph nodes. Three patients presented with fever. None of the cases had clinical and laboratory findings suggesting systemic lupus erythematosus. The original diagnoses of FNAC are listed in Table 1. Originally, none of the cases was diagnosed as or suspected to be KL, and all of the original cytologic diagnoses were non-specific: reactive hyperplasia in 4 cases and negative for malignant cells in 6 cases.

The cytological findings of KL are summarized in Table 2. Of a total of 10 cases, 5 cases had hypercellular smears, but the remaining cases were hypocellular. Karyorrhectic debris was focally observed in only 3 cases. Granular background material (Fig. 1A) was found in 7 cases, and cheese-like necrosis was seen in none of them. Crescentic histiocytes of variable numbers were found in 8 cases and were characterized by the presence of ec-

centrically placed crescentic nuclei and intracytoplasmic karyorrhectic debris (Fig. 1B). Acidophilic cells were demonstrated in all the 10 cases. Acidophilic cells had piknotic nuclei and distinct cytoplasm that was present as a pink colored condensed form as seen with hematoxylin and eosin stain (Fig. 1C) and orangeophilic with Papanicolaou stain. Acidophilic cells were easily observed in the cytologic smears, even with low power magnification and also in cases with very low cellularity and/or a dry artifact. No epithelioid histiocytes, giant cells, or neutrophils were noted in any of the KL smears. Histologically, all the cases of KL revealed patchy or confluent areas of necrosis associated with abundant extracellular karyorrhectic debris, numerous crescentic histiocytes and rare neutrophils (Fig. 1D).

Of a total of 10 cases of tuberculosis, the male to female ratio was 3 : 7, and their ages ranged from 34 to 51 years (mean, 42.2 years). The affected lymph nodes were all the cervical lymph nodes. The cytological findings of tuberculosis are summarized in Table 3. All the cases revealed hypercellular smears. Of a total of 10 cases, 9 cases were associated with a cheese-like necrotic background (Fig. 2A). Scattered or aggregated epithelioid histiocytes (Fig. 2A) were observed in 4 cases. Abundant karyorrhectic debris (Fig. 2B) was found in 6 cases. Crescentic histiocytes were not found in any of the cases. Variable numbers of acidophilic cells (Fig. 2C) were demonstrated in 6 cases. Abundant neutrophils (Fig. 2C) were noted in 8 cases. The comparison of cytological findings of KL and tuberculosis are summarized in Table 4. Histologically, all the cases of tuberculosis revealed extensive caseous necrosis admixed with several neutrophils and surrounded by epithelioid histiocytes (Fig. 2D).

Table 1. Patient's characteristics and original cytological diagnosis in patients with Kikuchi's lymphadenitis

Case No.	Sex/Age (yr)	Site of lymph node	Chief complaint	Original cytological diagnosis
1	F/15	Cervical	Palpable mass	Reactive hyperplasia
2	M/9	Cervical	Fever	NFMC
3	F/22	Cervical	Palpable mass	Reactive hyperplasia
4	F/24	Cervical	Palpable mass	Reactive hyperplasia
5	M/23	Cervical	Palpable mass	Reactive hyperplasia
6	M/17	Cervical	Palpable mass	NFMC
7	F/23	Cervical	Palpable mass	NFMC
8	M/16	Cervical	Fever and palpable mass	NFMC
9	M/22	Cervical	Fever and palpable mass	NFMC
10	F/29	Cervical	Palpable mass	NFMC

F, female; M, male; NFMC, negative for malignant cells.

Table 2. Cytological findings in cases of Kikuchi's lymphadenitis

Case No.	Cellularity	Background material	Karyorrhectic debris	Crescentic histiocytes	Acidophilic cells	Epithelioid histiocytes	Neutrophils
1	High	Granular	None	Many	Many	None	None
2	Low	Unremarkable	None	A few	Many	None	None
3	High	Granular	A few	Many	Many	None	None
4	High	Granular	None	Many	Many	None	None
5	High	Granular	None	Many	Many	None	None
6	High	Granular	None	A few	A few	None	None
7	Low	Unremarkable	None	None	A few	None	None
8	Low	Unremarkable	A few	A few	A few	None	None
9	Low	Granular	A few	A few	A few	None	None
10	Low	Granular	None	None	A few	None	None

DISCUSSION

Cytologically, the main differential diagnosis of KL includes tuberculosis, systemic lupus erythematosus, nonspecific reactive

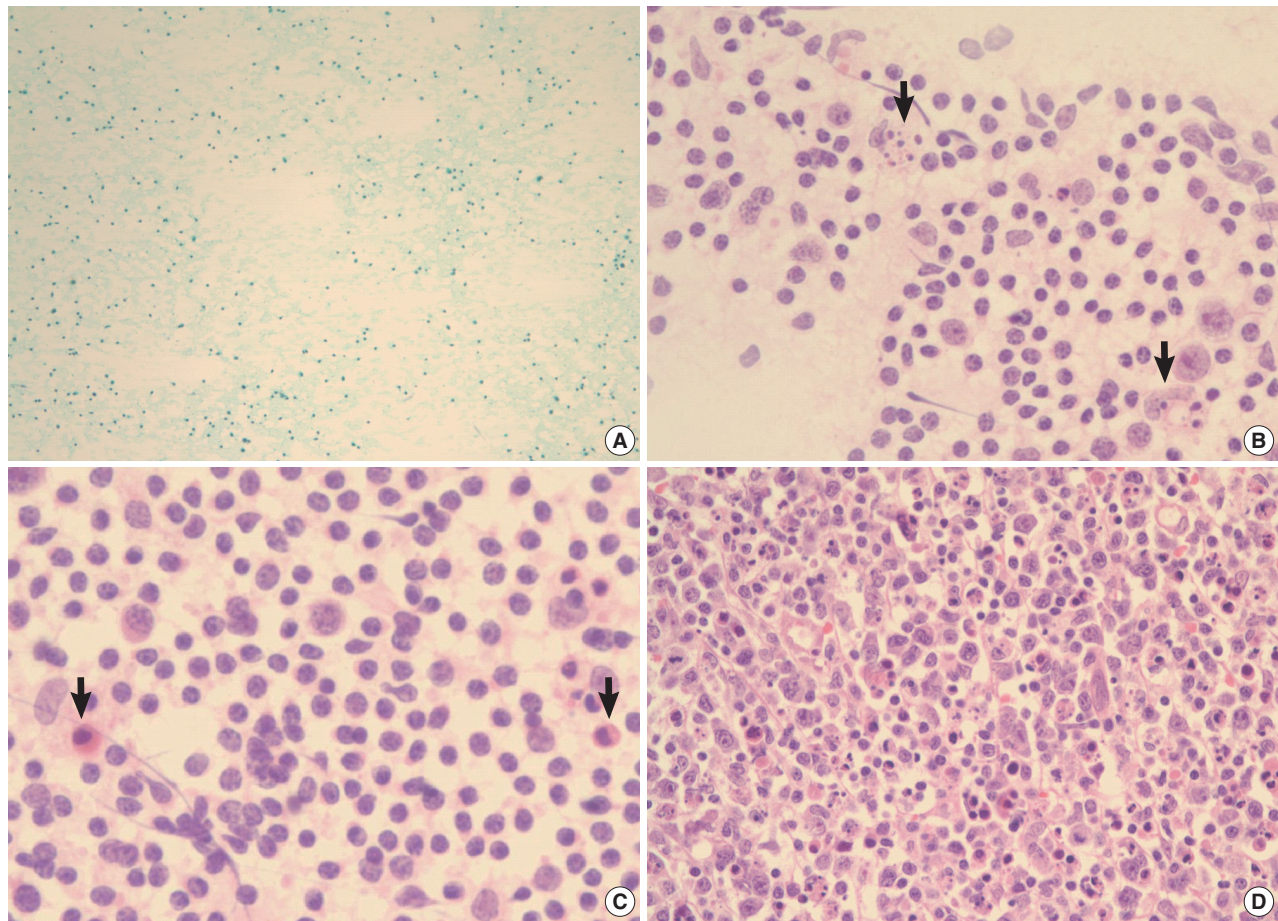


Fig. 1. Fine needle aspiration cytology of Kikuchi's lymphadenitis is characterized by granular background material (A), crescentic histiocytes (arrows) showing eccentrically placed crescentic or distorted nuclei and intracytoplasmic karyorrhectic debris (B) and acidophilic cells (arrows) showing piknotic nuclei and pink condensed cytoplasm (C). The corresponding histology reveals abundant crescentic histiocytes and karyorrhexis (D).

Table 3. Cytological findings in cases of tuberculosis

Case No.	Cellularity	Background material	Karyorrhectic debris	Crescentic histiocytes	Acidophilic cells	Epithelioid histiocytes	Neutrophils
1	High	Cheese-like	Many	None	Many	A few	Many
2	High	Cheese-like	Many	None	None	None	Many
3	High	Cheese-like	Many	None	Many	A few	Many
4	High	Cheese-like	None	None	None	None	None
5	High	Cheese-like	Many	None	Many	None	Many
6	High	Cheese-like	Many	None	Many	None	Many
7	High	Cheese-like	None	None	None	None	Many
8	High	Cheese-like	Many	None	Many	Many	Many
9	High	Cheese-like	None	None	A few	None	Many
10	High	Granular	None	None	None	Many	None

hyperplasia, and malignant lymphoma.^{5,6,9,11,15} The necrotizing form of KL may be difficult to distinguish from tuberculosis and systemic lupus erythematosus.¹⁶ Similar to the data of the present study, tuberculosis shares many characteristic cytological features of KL, such as the presence of necrotic material, kar-

yorhectic debris and acidophilic cells. However, the absence of neutrophils, multinucleated giant cells, and scattered or aggregated epithelioid histiocytes favors KL. The cytologic differentiation of KL from lupus lymphadenopathy may be very difficult or sometimes impossible.^{9,10} Clinical and laboratory data

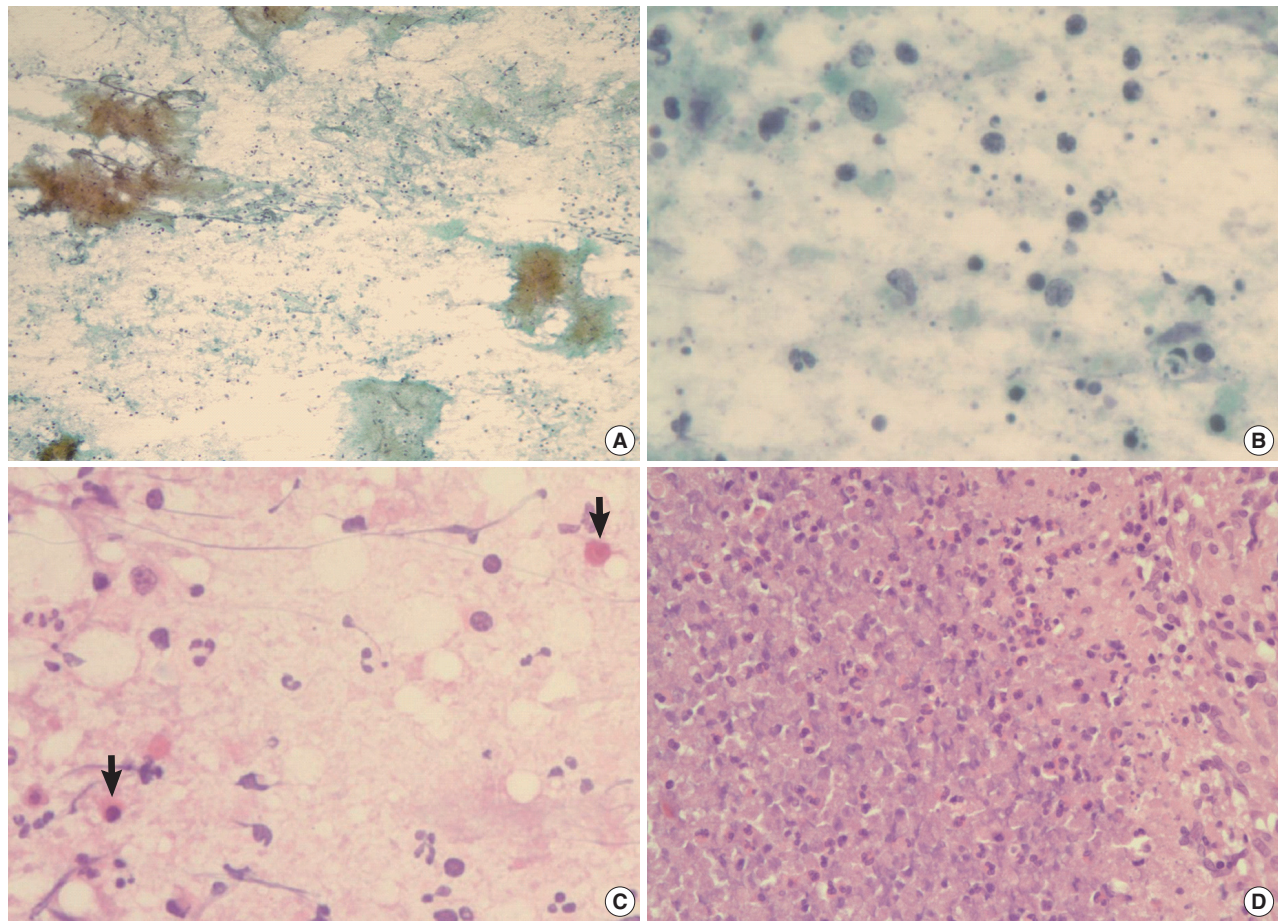


Fig. 2. Fine needle aspiration cytology of tuberculosis shows cheese-like necrosis with scattered epithelioid histiocytes (A), abundant karyorrhectic debris (B), acidophilic cells (arrows) and many neutrophils (C). The corresponding histology reveals extensive necrosis admixed with neutrophils and surrounded by epithelioid histiocytes (D).

Table 4. Comparison of cytological features of Kikuchi's lymphadenitis and tuberculosis

Cytologic features	Kikuchi's lymphadenitis (n = 10)	Tuberculosis (n = 10)
High cellularity	5	10
Granular background material	7	1
Cheese-like necrosis	0	9
Karyorrhectic debris	3	6
Crescentic histiocytes	8	0
Acidophilic cells	10	6
Epithelioid histiocytes	0	4
Neutrophils	0	8

are necessary for differential diagnosis between these two conditions.¹⁰ It is difficult to differentiate KL from nonspecific reactive hyperplasia because aspiration cytology has limitations in making a specific diagnosis. However, considering the data of the present study, the presence of acidophilic cells is a very sensitive and useful marker in distinguishing KL from nonspecific reactive hyperplasia. Abundant immunoblasts found in the pro-

liferative form of KL might be confused with malignant lymphoma, particularly with high-grade malignant lymphoma.^{11,15} None of our cases were confused with malignant lymphoma.

The pathogenesis of KL still remains unclear. However, apoptotic cell death appears to be the principal finding in the histogenesis of this disease.¹⁷ In the present study, all the cases revealed variable amounts of acidophilic cells on the cytological smear. The acidophilic cells corresponded to the apoptotic cells. In the present study, the acidophilic cells were easily recognized in the cytological smears because of their distinct cytoplasmic color, even with low power magnification and poor smear conditions. Thus, acidophilic cells might be very helpful in considering KL in the differential diagnosis. However, a considerable number of acidophilic cells were also observed in tuberculosis. Therefore, acidophilic cells may not be specific to KL, but they might be a very sensitive marker of necrotizing inflammation, including KL and tuberculosis, on the cytological smear.

Previously, Yoo *et al.*¹⁴ reported 30 cases of FNAC of KL, of

which only 5 cases were confirmed by subsequent histological examination and the rest of which were only diagnosed with cytology. They described that all the cases revealed hypercellular smear with abundant extracellular karyorrhectic debris and crescentic histiocytes. However, our study excluded the cases, which were diagnosed as KL with FNAC and did not undergo subsequent excisional biopsy. In the present study, we included only cases of FNAC of KL with subsequent histological confirmation. Unlike Yoo *et al.*'s study,¹⁴ our study revealed low cellularity in 5 out of 10 cases and inconspicuous extracellular karyorrhectic debris in 7 of them. It appeared that originally, the low cellularity and inconspicuous extracellular karyorrhectic debris led to difficulties in making a correct cytologic diagnosis in our cases.

Crescentic histiocytes have been known as one of the most characteristic cells in KL.^{11,14,15} They should be strictly differentiated from tingible body macrophages, which are predominantly found in the reactive germinal centers. The crescentic histiocytes have eccentrically placed crescentic or distorted nuclei with ingested nuclear debris.^{6,11} In contrast, tingible body macrophages usually have centrally located, round to ovoid nuclei with ingested debris. Tsang and Chan¹¹ reported that very few phagocytic histiocytes with crescentic nuclei were observed in 2 out of 50 cases of tuberculosis or malignant lymphoma. In the present study, crescentic histiocytes were noted in 80% of KL in variable degrees, but they were not observed in any cases of tuberculosis. Therefore, crescentic histiocytes may be a sensitive and considerably specific marker for KL.

Karyorrhectic debris has also been known as one of the characteristic cytological feature of KL.^{5,8,13,15} The karyorrhectic debris could be confused with neutrophils. Karyorrhectic debris are extracellular, and irregularly shaped nuclear fragments without accompanying the cytoplasm, whereas neutrophils show well-formed segmented nuclei with distinct cytoplasm. In the present study, however, karyorrhectic debris was observed only in 3 out of 10 cases, in which the karyorrhectic debris was even focally present. In the present study, the incidence and degree of karyorrhectic debris in FNAC of KL might be lower than that in routine histology, considering that all the cases histologically revealed prominent patchy or extensive necrotizing inflammation. The lack of karyorrhectic debris in FNAC may lead to difficulties in diagnosing KL using this criterion alone.

In the present study, all the KL cases revealed an unremarkable or granular background with no cases of cheesy necrotic background. This is consistent with the previously reported cytological features of KL.¹¹ On the other hand, 9 out of 10 cases

of tuberculosis were associated with cheese-like necrotic background. Therefore, the presence of cheese-like necrotic background can exclude the possibility of KL and suggest tuberculosis.

Like several previous reports,⁵ in the present study, neutrophils, scattered or aggregated epithelioid histiocytes, and Langerhans' giant cells were not found in all the cases of FNAC of KL. In contrast, neutrophils and epithelioid histiocytes or Langerhans' giant cells were noted in 80 and 40% of FNAC of tuberculosis, respectively. The high incidence of neutrophils and low incidence of epithelioid histiocytes, or Langerhans' giant cells seems to reflect the fact that our cases of tuberculosis were associated with extensive necrosis. The presence of neutrophils, epithelioid histiocytes or Langerhans' giant cells can exclude the possibility of KL and favor tuberculosis in the differential diagnosis.

Because KL has been known to subside spontaneously, lymph node excision is not needed following cytological diagnosis.^{2,14} All the cases included in the present study were not diagnosed as or suspected to be KL, and all the patients underwent unnecessary excision of lymph node for histological confirmation. Most of the cases in the present study did not reveal full-blown typical cytological features of KL and a half of KL cases showed hypocellular smear; however, the clinical features, especially cervical lymph node enlargement in young adults, as well as the sensitive cytological markers as described above such as, acidophilic cells and crescentic histiocytes, might lead to the consideration of KL as a diagnosis. It is important to make a correct cytological diagnosis with FNAC to avoid unnecessary excision and guide proper management.

In conclusion, our study suggests that FNAC in combination with clinical features may be useful in suspecting KL. The presence of acidophilic cells may be the most sensitive marker of KL on FNAC, but they are not specific to KL. However, the presence of crescentic histiocytes may be a sensitive and considerably specific marker of KL. The important cytologic features distinguishing tuberculosis from KL are thought to be cheese-like necrosis admixed with neutrophils and epithelioid histiocytes.

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