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Original Article

Comparison of clinical and pathological features of lymph node tuberculosis and histiocytic necrotizing lymphadenitis

Jin-sun Yang[1]*, Zhi-xiang Du[2]*

[1] Department of Infectious Diseases, Affiliated Yijishan Hospital of Wannan Medical College, Wuhu, Anhui 241001, China
[2] Department of Infectious Diseases, Taizhou People's Hospital, Taizhou, Jiangsu 225300, China

* Both authors contributed equally to this work.

Abstract

Introduction: The aim of this study was to investigate the basis for a differential diagnosis of lymph node tuberculosis and histiocytic necrotizing lymphadenitis.

Methodology: This study selected 85 cases of lymph node tuberculosis (Group A patients) and 26 cases of histiocytic necrotizing lymphadenitis (Group B patients). The clinical and pathology features on both groups were analysed.

Results: The Group A patients were older than the Group B patients ($t = 5.233$, $P < 0.01$); The Group B patients had less tuberculosis exposure history ($x^2 = 4.279$, $P < 0.01$), and a higher frequency of tenderness ($\chi^2 = 8.109$, $P < 0.01$) and fever ($x^2 = 31.923$, $P < 0.01$). The Group A patient group had a higher WBC level ($t = 2.980$, $P < 0.01$) and lower serum ALB ($t = 5.508$, $P < 0.01$); As seen through ultrasound imaging, Group B patients had more clear boundaries (70.59%), higher low-echo rates (82.36%) and low calcification rates (0%), Group A patients for whom these rates was 25.76%, 40.91% and 25.76% respectively. In terms of pathology data, the main manifestations of Group A patients were granulomatous inflammation with caseous necrosis, multinuclear giant cell reaction, and in some cases, acid-fast bacilli smears (+). In Group B patients, there were instances of coagulative necrosis surrounded by foam-like tissue cells without neutrophil infiltration.

Conclusion: We found that the epidemiological history, clinical symptoms, laboratory examinations, ultrasound imaging and changes in pathology are very important for the identification of lymph node tuberculosis and histiocytic necrotizing lymphadenitis.

Key words: Lymph node tuberculosis; histiocytic necrotizing lymphadenitis; clinical features; ultrasonographic features; pathological features.

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Introduction

Tuberculosis (TB) remains a serious public health issue in China, despite the availability of highly efficacious treatment for decades. According to the World Health Organization (WHO) report on global Tuberculosis control (2017), China had the world's second largest TB epidemic with approximately one million new cases, accounting for 8.6% of global incidence [1,2]. According to some recent reports, approximately 19.3%–39.3% of patients present with extra-pulmonary tuberculosis (EPTB) or EPTB concurrent with pulmonary involvement in active TB disease[3-5]. With the increasing prevalence of HIV infection, the proportion of EPTB among all TB cases has been expanding [6,7].

Lymph node tuberculosis is a specific lymphadenitis caused by *Mycobacterium tuberculosis (Mtb)* infection, and is one of the most common forms of EPTB. Histiocytic necrotizing lymphadenitis is a self-limited benign disease and is also known as Kikuchi- Fujimoto disease which was first reported independently by the Japanese scholars Kikuchi and Fujimoto in 1972 [3]. The disease is usually limited to lymph nodes; however, its presence in the skin, liver, spleen and even the nervous system has been reported [8,9].

These two diseases show similar clinical manifestations such as fever, lymphadenopathy, local pain or tenderness, and respond with similar ineffectiveness to general anti-inflammatory treatment [10]. Therefore, it is important to identify these two diseases in clinical practice. In this study, we analyzed the differences in clinical manifestations, laboratory tests, ultrasound images and pathological features between lymph node tuberculosis and histiocytic necrotizing lymphadenitis.

Methodology

Patients

Eighty-five cases of lymph node tuberculosis (Group A) and 26 cases of histiocytic necrotizing lymphadenitis (Group B) were selected. These cases were treated at Yijishan Hospital of Wannan Medical College from June 2012 to October 2016. Local ethics committee approval was obtained for the study. Our research was recognized by the ethics committee, and an ethic certification was obtained. Informed consent was acquired by signature for all patients in this study. All the researchers adhered to the Declaration of Helsinki. The diagnosis of lymph node tuberculosis requires observations of comprehensive clinical manifestations, laboratory tests, an examination of pathology and demonstrated anti-tuberculosis treatment efficacy. Histiocytic necrotizing lymphadenitis was diagnosed on the basis of clinical manifestations, laboratory tests, typical changes in pathology and responses to glucocorticoids.

Treatment methods and efficacy judgement

Patients with lymph node tuberculosis were treated regularly with the 2HRZE/7HR anti-tuberculosis programme which was adjusted according to each patient's specific condition. If necessary, surgical incision drainage was implemented. Patients with histiocytic necrotizing lymphadenitis were mainly supported by symptom treatment, and glucocorticoid treatment was used when necessary and gradually reduced until it discontinuation.

Both groups were followed regularly after discharge. The efficacy criteria were identified as follows. First, the symptoms were relieved and at the end of treatment, if the enlarged lymph nodes completely disappeared, then the condition was judged as cure. Second, the symptoms improved, and at the end of treatment, if the enlarged lymph nodes were smaller or fewer in number than before, then the condition was judged as improved. Third, the symptoms progressed and at the end of treatment, if the enlarged lymph nodes were not reduced or has grown even larger, then the condition was judged in progression. Recurrence referred to patients who experienced recurrent lymphadenopathies, which indicates a diagnosis of the same disease at least 1 year after the previous cure. Patients with recurrence of histiocytic necrotizing lymphadenitis were also treated with glucocorticoids, which were gradually reduced until they were discontinued. Two patients with lymphatic tuberculosis were re-treated, one with isoniazid and rifampicin (MDR) and one with the 6SLfxPtoZE/12LfxPtoZE anti-tuberculosis regimen [11].

General survey

The clinical manifestations, laboratory findings, ultrasound images and pathology data of both groups were collected for a retrospective analysis. The general conditions included gender, age, TB at other sites and history of tuberculosis exposure. The clinical manifestations included enlarged lymph nodes, lymph node tenderness, fever, night sweats and weight loss. The laboratory tests included white blood cells (WBC), albumin (ALB), erythrocyte sedimentation coefficient (ESR), C-reactive protein (CRP) and purified protein derivative (PPD) test. The ultrasound imaging included

Table 1. The Clinical characteristics of the two groups.

Value	Group A	Group B	Test value	P value
N	85	26		
Gender（male/female）	30/55	8/18	$\chi2 = 0.181$	> 0.05
Age（years）	42.7 ± 15.4	28.4 ± 11.1	t = 5.233	< 0.01
Other sites of tuberculosis（W/WO）	10/75	0/26	$\chi2 = 2.080$	> 0.05
Tuberculosis exposure history（W/WO）	23/62	2/24	$\chi2 = 4.279$	< 0.05
Incidence site（neck/other site）	79/6	25/1	$\chi2 = 0.017$	> 0.05
Incidence side（single /double）	71/14	8/18	$\chi2 = 2.561$	> 0.05
Tenderness（W/WO）	26/59	10/16	$\chi2 = 8.109$	< 0.05
Fever（W/WO）	8/77	10/16	$\chi2 = 31.923$	< 0.01
Night sweats（W/WO）	15/70	2/24	$\chi2 = 0.851$	> 0.05
Weight loss（W/WO）	15/70	1/25	$\chi2 = 2.057$	> 0.05
WBC (×109/L)	5.006 ± 2.202	3.627 ± 1.514	t = 2.980	< 0.01
ALB (g/L)	35.871 ± 5.545	40.910 ± 3.513	t = 5.508	< 0.01
ESR(mm/h)	39.841 ± 22.596	34.871 ± 17.133	t = 0.916	> 0.05
CRP (g/L)	18.107 ± 8.285	18.263 ± 10.394	t = 0.036	> 0.05
PPD test*(positive/negative)	52/16	2/15	$\chi2 = 24.58$	< 0.01

*Group A = lymph node tuberculosis patients; Group B = histiocytic necrotizing lymphadenitis patients; W = with, WO = without; There are only 68 cases of Group A and 17 cases of Group B conducted PPD test. t-tests and Chi-square test were used for comparative analysis.

clear/ambiguous boundaries, echo changes and calcification. The pathology data included specimen microscopy, acid-fast staining smears and immunohistochemistry. The prognosis included the curative effect and recurrence rate after treatment for at least 1 year.

Statistical analysis

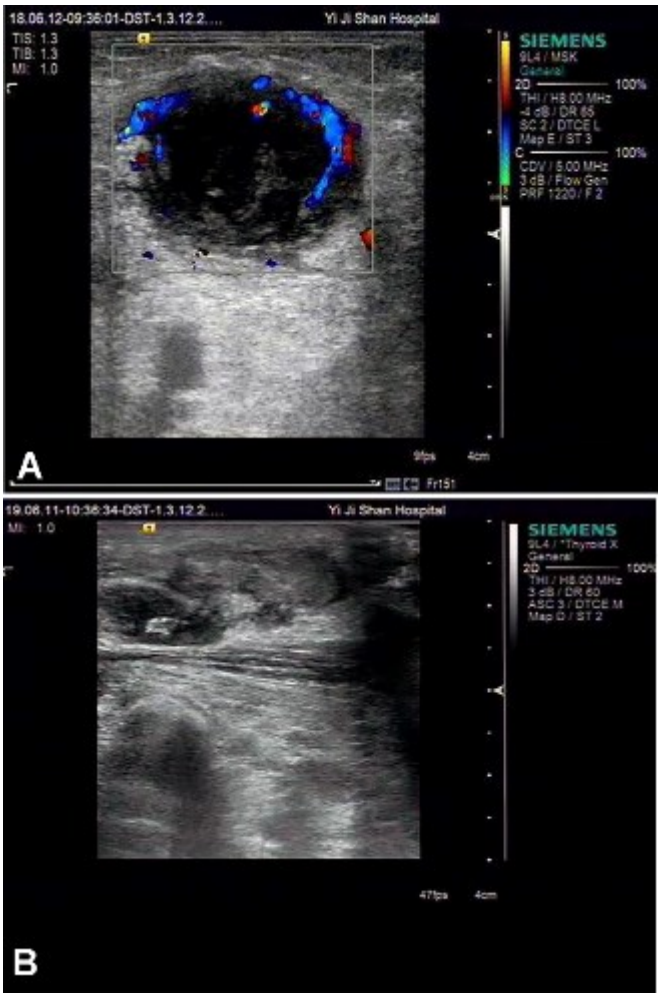
Data were analyzed by the SPSS software package for Windows (version 18.0; SPSS Inc., Chicago, IL, USA). Quantitative clinical data (age, WBC, ALB, ESR and CRP test results) followed a Gaussian distribution which is represented by means ± SD ($\bar{x} \pm s$), and t-tests were used for the comparison between the lymph node tuberculosis group (Group A) and the histiocytic necrotizing lymphadenitis group (Group B). Frequencies and percentages were used to describe the nonparametric variables and the comparisons between these groups were based on a Chi-square test. A P value of < 0.05 was considered to show a statistically significant difference.

Results

Clinical characteristic and Laboratory results

This study was involved 111 subjects that included 85 cases of lymph node tuberculosis (Group A) and 26 cases of histiocytic necrotizing lymphadenitis (Group B). The clinical characteristics of the two groups are shown in Table 1. The patients in Group B were significantly younger (28.4 ± 11.1 years) than those Group A (42.7 ± 15.4, $P < 0.01$), and most of the Group A patients had a history of tuberculosis exposure history ($\chi^2 = 4.279$, $P < 0.05$) . There were no statistically significant differences between the two groups regarding sex or other sites of tuberculosis ($P > 0.05$). The frequency of tenderness for Group B was higher (61.54%) than it was for Group A (30.59%, $P < 0.05$). Consistent with tenderness, the fever frequency for Group B was significantly higher (61.54%) than that in Group A (9.41%, $P < 0.01$). There were no statistically significant differences in incidence sites, sides of the body affected, reports of night sweats and weight loss between the two groups.

Figure 1. The typical image from the ultrasonography of lymph node tuberculosis. (A). The typical image from the ultrasonography of lymph node tuberculosis showed a fuzzy boundary, low or mixed internal echo and calcification. (B). The typical images from the ultrasonography of histiocytic necrotizing lymphadenitis showed a clear boundary, low internal echo and no calcification.



The levels of WBC for Group A patients were significantly lower than those in Group B patients ($t = 2.980$, $P < 0.01$). Group A patients had lower ALB levels than Group B patients ($t = 2.980$, $P < 0.01$). From Group A, 68 patients underwent the PPD test, which resulted in 52 positive cases and 16 negative cases, while from Group B 17 patients underwent the PPD

Table 2. Ultrasound imaging characteristics of the two groups.

Value	Group A	Group B	Test value	P value
N	66	17		
Boundary (clear/fuzzy)	19/47	12/5	$\chi2 = 10.094$	< 0.01
Internal echo (low/mix/high)	27/29/10	2014/2/1	$\chi2 = 9.323$	< 0.01
Calcification	17/49	0/17	$\chi2 = 4.039$	< 0.05

*Group A = lymph node tuberculosis patients; Group B = histiocytic necrotizing lymphadenitis patients; Chi-square test were used for comparative analysis.

test, which resulted in only 2 positive cases and 15 negative cases ($\chi^2 = 24.576$, $P < 0.01$). The laboratory results of the two groups are shown in Table 1.

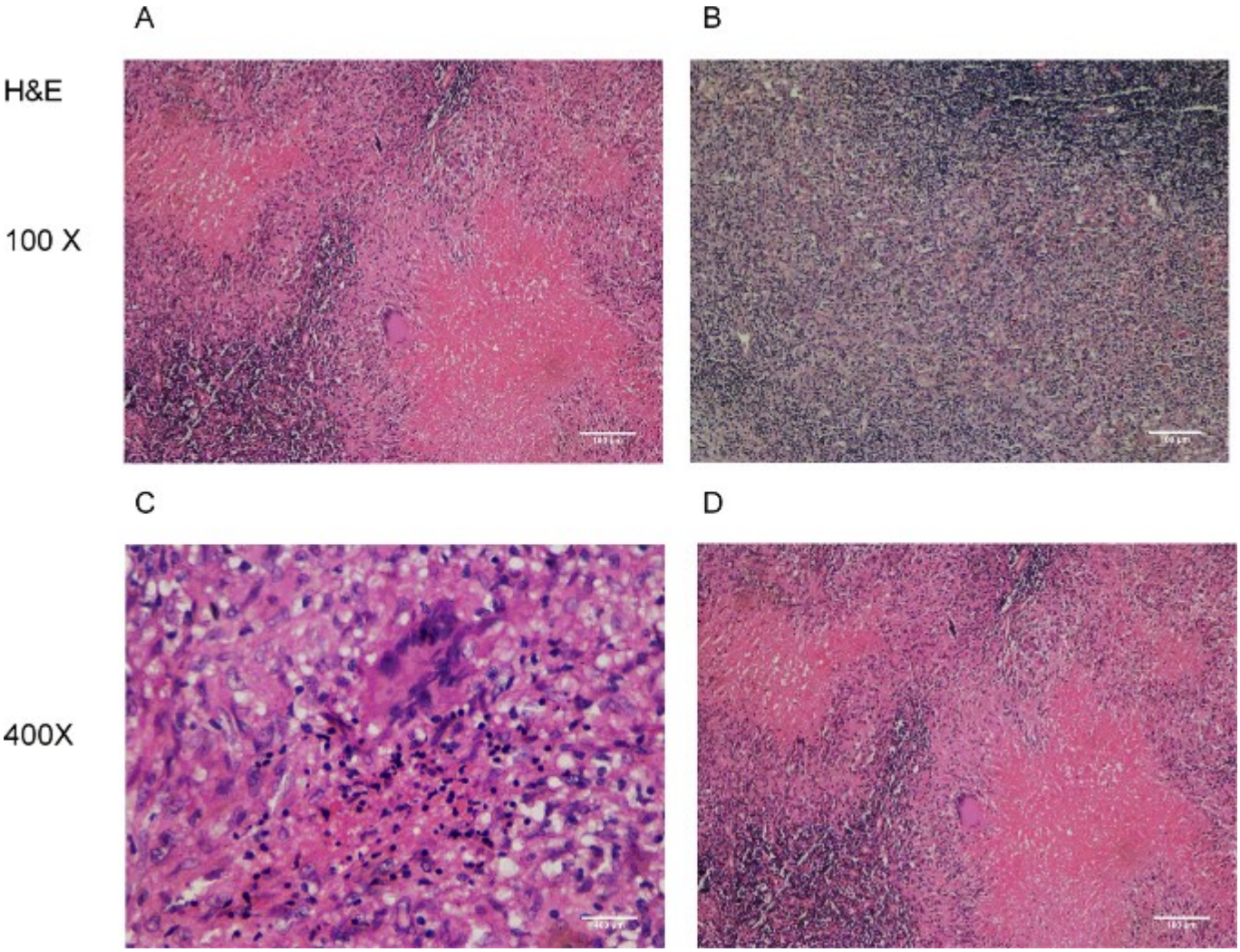
Ultrasound imaging

In the 66 cases from Group A that underwent ultrasonography, only 19 lesions had clear boundaries, while in 17 cases from Group B that underwent ultrasonography, 12 had clear boundaries ($\chi^2 = 10.094$, $P < 0.01$). Compared with those of Group A, most of the Group B lesions had low echo ($\chi^2 = 9.323$, $P < 0.01$), while none of the Group B lesions were accompanied by calcification ($\chi^2 = 4.039$, $P < 0.05$). The ultrasound images for the two groups were obviously different (Table 2).

Pathology data

An examination of lymph node tuberculosis pathology showed granulomatous inflammation, caseous necrosis and multinuclear giant cell reaction (Figure 2). Fifteen cases showed acid-fast staining smears (+), with a positive rate of 17.6% (15/85) (Figure 3). As shown in Figure 2, an examination of histiocytic necrotizing lymphadenitis histopathology revealed that the normal structure of the lymph nodes disappeared. There was a large amount of coagulative necrosis near the accessory cortex without neutrophil infiltration and many foam-like tissue cells around the necrotic area. The specimens for pathology testing of 16 patients in Group B were stained using immunohistochemistry. CD68-positive macrophages aggregated in all 16 tissues (Figure 4). Nine cases were

Figure 2. H&E staining of Lymph node TB and Kikuchi's disease.



(A). shows typical H&E staining of tuberculosis specimens (×100). (C) showed typical H&E staining of tuberculosis specimens (×400). (B**)** showed typical H&E staining of histiocytic necrotizing lymphadenitis (×100). (D) showed typical H&E staining of histiocytic necrotizing lymphadenitis (×400).

MPO (+), 14 cases of residual germinal center B lymphocytes were CD20 (+) and 9 cases were Ki-67 positive and scattered (approximately 5%-10%).

Treatment results

After anti-tuberculosis treatment, 59 cases were cured, 24 cases had improved and 2 cases were unhealed. Among the 26 cases of histiocytic necrotizing lymphadenitis, 24 cases were cured, 2 cases had improved and 0 cases were unhealed. The efficacy of the two groups was tested by use of the Kruskal-Wallis H test, and no significant differences were found between the two groups ($\chi^2 = 1.853$, $P = 0.173$).

Twenty-eight patients with lymph node tuberculosis and 16 patients with histiocytic necrotic lymphadenitis participated in the follow-up prognosis for at least 1 year after healing. Two patients from Group A and 1 patient from Group B experienced recurrence. The recurrence rates were 7.14% and 12.5%, respectively, and there were no significant differences between the two groups ($\chi^2 = 0.000$, $P = 1.000$).

Figure 3. Tissue acid-fast staining results. The slice showed positive anti-acid staining of lymph node tuberculosis (× 1000).

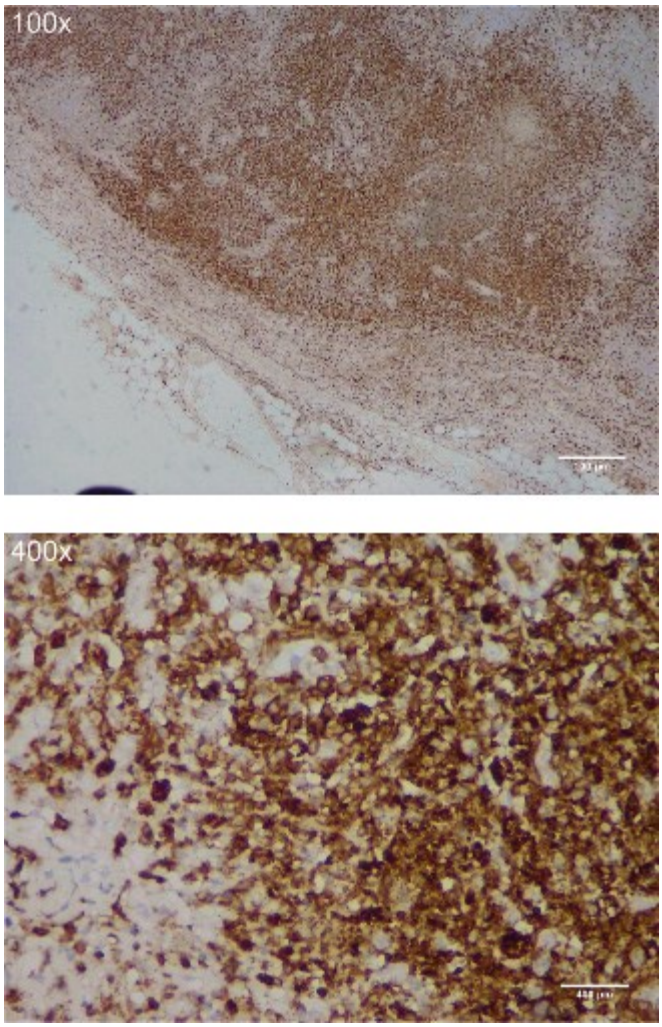
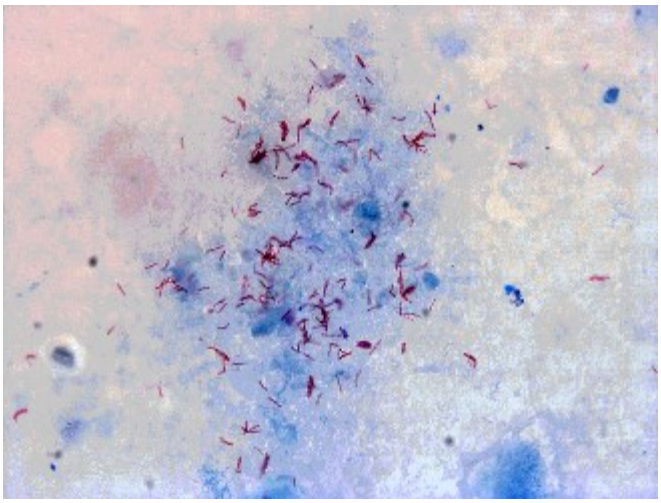


Figure 4. Histiocytic necrotizing lymphadenitis section stained by CD68 (IHC). CD68-positive macrophages aggregated in tissues



Discussion

Tuberculosis remains a major health problem in some countries, especially developing countries. The inefficacy of the BCG vaccine, false-positive screening tests, non-compliance with treatment regimens, complexity of MTB, delays in developing new treatment plans and high incidence of HIV are the reasons for the widespread epidemic of tuberculosis in developing countries [12]. China is also a developing country and has a high incidence of tuberculosis. Lymph node tuberculosis is one of the most common types of extra-pulmonary tuberculosis and is not clinically rare [13]. In addition, histiocytic necrotizing lymphadenitis mostly occurs in eastern Asian countries, and domestic reports have also increased every year [14]. The incidence of both diseases is low. However, the clinical responses of histiocytic necrotizing lymphadenitis is very similar to that of lymph node tuberculosis. Early diagnosis is very important for the treatment of the two diseases, especially in endemic areas of tuberculosis such as China. Physician awareness of the two diseases is the key to timely diagnosis, minimizing unnecessary evaluations and rendering inappropriate treatment [15].

Combined in the data presented in this paper, the number of patients with lymph node tuberculosis is greater than the number of patients with histiocytic necrotizing lymphadenitis treated in our hospital. There was no significant difference in gender between the

people with the two diseases, and the male to female ratio was 1:1.83 (30/55), and 1:2.25 (8/18) for lymph node tuberculosis and histiocytic necrotizing lymphadenitis, respectively. Lymph node tuberculosis mainly occurs in young and middle-aged people, at an average age of 42.7 years, which is close to the average age of participants from another study [16]. However, the average age of patients with histiocytic necrotizing lymphadenitis is 28.4 years, and there were significant differences between the two groups, suggesting that patients with histiocytic necrotizing lymphadenitis are relatively younger.

Both of these diseases usually occur in the neck and mainly on one-side of the body. There was no significant difference in the incidence site or in the side of occurrence between the two groups, a finding that is basically consistent with other relevant reports [17]. Our study shows that 11.8% (10/85) of patients with Lymph node tuberculosis have compilations with that include other sites of tuberculosis, while no other sites of tuberculosis were found in patients with histiocytic necrotizing lymphadenitis. However, the difference between the two groups was not statistically significant, which suggests that the presence of tuberculosis in other sites cannot be used as a basis for a differential diagnosis of TB. There were also no significant differences in reports of night sweats and weight loss between the two groups, indicating that these symptoms do not distinguish the two diseases. The incidence of tenderness and fever in patients with lymph node tuberculosis and those with histiocytic necrotizing lymphadenitis were 30.6% (26/85) and 61.5% (16/26) and 9.4% (8/85) and 61.5% (16/26), respectively. These significant differences show that the incidences of tenderness and fever are significantly higher in patients with histiocytic necrotizing lymphadenitis than those with lymph node tuberculosis. In terms of tuberculosis exposure history, 27.1% (23/85) of patients with lymph node tuberculosis had positive exposure, while only 7.7% (2/26) of patients with histiocytic necrotizing lymphadenitis had postive exposure. These finding suggest that patients with a history of tuberculosis exposure are more likely to have lymph node tuberculosis. Therefore, tenderness, fever and epidemiological history should be emphasized in strategies to identify these two diseases.

In terms of laboratory tests, the data from this study show that there was a statistically significant difference between the two groups regarding routine WBC tests. The WBC of patients with lymph node tuberculosis was at a normal level, but it was below the lower limit of normal in patients with histiocytic necrotizing lymphadenitis. In terms of serum albumin, there was also a significant difference between the two groups. The ALB in patients with histiocytic necrotizing lymphadenitis was at a normal level, while it was below the lower limit of normal in patients with lymph node tuberculosis. This finding may be related to the long course of tuberculosis and the long-term depletion of albumin. The positive rate for the PPD test for patients with lymph node tuberculosis was 76.5% (52/68), and it was 11.8% (2/17) for patients with histiocytic necrotizing lymphadenitis, a significant difference. There were no significant differences between the ESR and CRP data of the two groups. The above results suggested that the WBC, serum ALB and PPD tests can be used in the laboratory to identify the two diseases.

Ultrasound images in the present study showed that edge-blurring, mixed echo or hyperechoic and calcified lesions are consistent with a diagnosis of lymph node tuberculosis. The necrotic lymph nodes are characterized by relatively sharp edges, low echo and no calcification [18]. Therefore, ultrasound imaging is helpful for a differential diagnosis of the two diseases. However, different stages of the disease and different experience levels of the physicians capturing the images may affect the ultrasound images; therefore, we must emphasize the importance of dynamic follow-up.

Whether it is lymph node tuberculosis or histiocytic necrotizing lymphadenitis, histopathological examination is the gold standard for diagnosis [19,20]. The characteristic manifestation of lymph node tuberculosis is caseous necrosis, which appears through red-stained granularity in HE stains, with neutrophil infiltration; surrounded by granuloma formation and by multinuclear giant cell reactions. A positive acid-fast smear for histopathology testing confirmed the diagnosis; however, the positive rate of acid-fast staining was not high (17.6%, 15/85). The pathological features of histiocytic necrotizing lymphadenitis include loss of normal lymph node structure; and coagulation necrosis with large amounts of nuclear debris but little or no neutrophil infiltration. The features of immunohistochemical stains for histiocytic necrotizing lymphadenitis are as follows: tissue cells cluster together and are often CD68 positive. MPO positive, and CD20 positive in germinal centre cells and Ki-67 positive scattering is also observed. Above all, diagnosis of pathology is the most important measure to identify lymph node tuberculosis and histiocytic necrotizing lymphadenitis.

Both lymph node tuberculosis and histiocytic necrotizing lymphadenitis are benign diseases. The overall curative effect is available, and there is no

significant difference in judgement efficacy between the two groups. However, both diseases will recur, and the recurrence rate for lymph node tuberculosis and histiocytic necrotizing lymphadenitis at 1 year is 7.14% and 12.5%, respectively, so clinical attention must be paid to them [21].

In summary, the clinical manifestations of lymph node tuberculosis and histiocytic necrotizing lymphadenitis are similar; however, the epidemiological history, laboratory examinations, ultrasound imaging and changes in pathology show characteristics that distinguish from each other. Therefore, a comprehensive analysis of the above results is necessary for differential diagnosis of these two diseases.

The limitations of our study are as follows: 1. The samples included in this study were not able to fully represent all significant differences between the two populations. Therefore, this study requires a longer study, a larger central sample dataset for statistical analysis, and more in-depth research. 2. This study only compares the clinical manifestations, laboratory tests result, changes in pathology and anti-tuberculosis efficacy of the two diseases, but the pathogenesis of the two diseases was not studied. In the future, we will conduct further research on the above issues.

Conclusion

In this study, we found that the epidemiological history, clinical symptoms, laboratory examinations, ultrasound imaging and changes in pathology are very important for the identification of lymph node tuberculosis and histiocytic necrotizing lymphadenitis.

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Authors' contribution

All authors met the four criteria for authorship contribution based on the recommendations of the international committee of medical journal editors. The two authors contributed equally to this work.

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Corresponding author
Jin-sun Yang
Department of Infectious diseases, Affiliated Yijishan Hospital of Wannan Medical College, zheshan street, NO 2, 241001, Wuhu, Anhui, China.
Phone: 0553-5739406
Fax: 0553-5738279
Email: yangjinsun999999@sohu.com

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