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ORIGINAL RESEARCH

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A retrospective study of 134 patients with cervical region Kikuchi–Fujimoto disease

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Abstract

Background: To explore the clinical and laboratory features, therapy and prognosis of Kikuchi–Fujimoto disease (KFD) in the cervical region.

Methods: We retrospectively reviewed the medical records of 134 patients who were diagnosed and treated with KFD from January 2000 to May 2022 in Fujian Medical University Union Hospital (Fujian, China). Their clinical characteristics, affected lymph node size, imaging examinations, and laboratory study results were analyzed.

Results: The mean patient age was 24.9 years, and the male–female ratio was 1:1.73. Fever (55.2%, $n = 74$) was the most common clinical manifestation. Leukopenia (49.3%) was the commonest reported laboratory abnormality. A majority (65.7%) of the 134 patients presented with bilateral nodal involvement.

Conclusion: KFD should be considered as a possible diagnosis in a female patient under the age of 30 presenting with cervical lymphadenopathy, fever, leukopenia, and elevated LDH.

Level of Evidence: 4.

KEYWORDS
cervical lymphadenopathy, Kikuchi–Fujimoto disease, leukopenia, systemic lupus erythematosus

1 | INTRODUCTION

The majority of patients with cervical lymphadenopathy initially visit the otolaryngology department. The causes of cervical lymphadenopathy are complex and include tuberculous lymphadenitis, malignant lymphoma, systemic lupus erythematosus (SLE). Kikuchi-Fujimoto disease (KFD), also known as histiocytic necrotizing lymphadenitis (HNL), is a rare but increasingly recognized cause of cervical lymphadenopathy. KFD was first described in 1972 separately by Kikuchi and Fujimoto et al.[1,2] However, as reports of this disease are predominantly published in the pathological literature and scarcely reported in the otolaryngology literature, many otolaryngologists are probably unaware of this condition.[3] With an increasing number of reported clinical cases, otorhinolaryngologists must be aware of the manifestations of this disease, clinical course, and the potential for confusion with other diseases.

2 | MATERIALS AND METHODS

A list of in-patients with discharge diagnosis of KFD from January 2000 to May 2022 was retrieved from an electronic medical database in Fujian Medical University Union Hospital (Fujian, China). All patients had histologically proven disease by an excisional biopsy of a lymph node. The histological findings may vary but generally have

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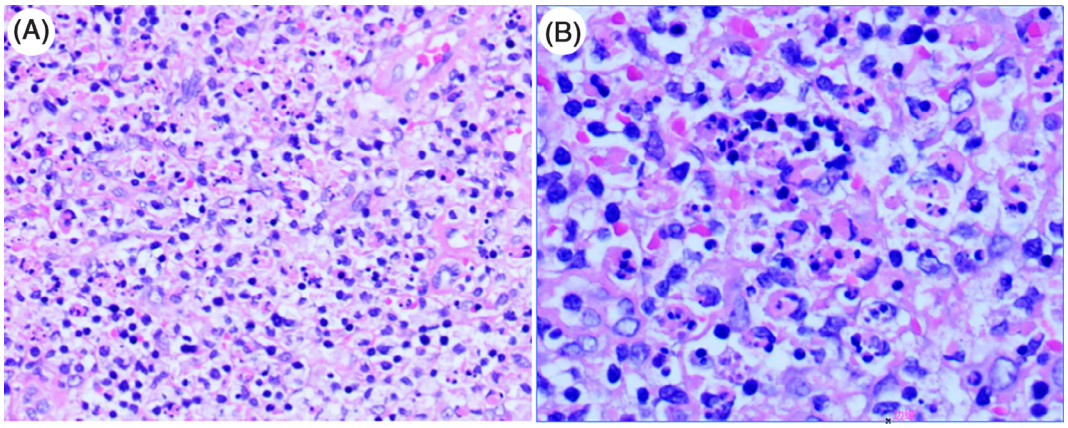

FIGURE 1 (A) Crescentic histiocytes having eccentrically located nuclei are observed (original magnification X200). (B) Cellular disintegration, the presence of abundant histiocytes engulfing nuclear debris (original magnification X400).

TABLE 1 Clinical features of Kikuchi–Fujimoto disease.

	No. of patients (%)
N	134
Gender, *n*	
Male	50 (37.3)
Female	84 (62.7)
Median age, year	24 (17.9)
Fever (>37.5°C), *n*	74 (55.2)
Tenderness, *n*	33 (24.6)
Rash, *n*	21 (15.7)
Arthralgia, *n*	8 (6.0)

TABLE 2 Laboratory characteristics of the cases.

	No. of patients (%)
↓Leukocyte	66/134 (49.3)
↓Hemoglobin	26/134 (19.4)
↑ALT	15/134 (11.2)
↑AST	22/134 (16.4)
↑ESR	51/134 (38.1)
↑LDH	59/134 (44.0)
↑Ferritin	29/76 (38.2)
ANA(+)	29/117 (24.8)

Abbreviations: ALT, glutamic-pyruvic transaminase; ANA, antinuclear antibody; AST, glutamic-oxalacetic transaminase; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase.

the following criteria[4]: (1) patchy irregular areas of eosinophilic necrosis in the paracortex and/or cortex, (2) pronounced fragments of nuclear debris ('nuclear dust') with numerous histiocytes, some with crescentic nuclei, are distributed irregularly throughout the area of necrosis, (3) absence of granulocytes and paucity of plasma cells, (4) clusters of plasmacytoid dendritic cells, and (5) numerous immunoblasts (transformed lymphocytes, predominantly of T cell phenotype) (Figure 1). Clinical characteristics, affected lymph node size, imaging examinations, and laboratory study results were obtained by consulting medical records and contacting patients by telephone. All procedures performed in this study involving human participants were following the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments.

3 | RESULTS

3.1 | Patient characteristics

One hundred and thirty-four patients were included in the study. Detailed clinical characteristics of the study patients are reported in Table 1. The mean patient age was 24.9 years (range, 4–64 years), and the male–female ratio was 1:1.73. Thirty-three cases (24.6%) involved pediatric patients younger than 16 years. Sixty-six patients (73.9%) were under the age of 30. The most common symptoms of the patients were fever, lymph node tenderness, or rashes, with a median number of 1 symptom per patient. One patient presented with meningitis. The length of follow-up ranged from 1 to 256 months. In our study, 1 patient had known SLE, 3 had a concomitant diagnosis of SLE, and 1 developed SLE in the year following the diagnosis of KFD. Clinical recurrence was observed in 13 patients (21.3%) with a time to relapse of 30.2 months (12–160).

3.2 | Laboratory examinations

Blood work most commonly demonstrated a mild leukopenia (49.3%) and elevated lactate dehydrogenase (LDH) (44.0%), as well as elevated erythrocyte sedimentation rate (ESR) (38.1%). None had severe leukopenia (white blood count of <2000/mm^3). Only some of the included patients were tested for antinuclear antibody (ANA) and ferritin. A significant titer (>1/320) of ANA was present in 24.8% cases and elevated ferritin in 38.2% cases (Table 2).

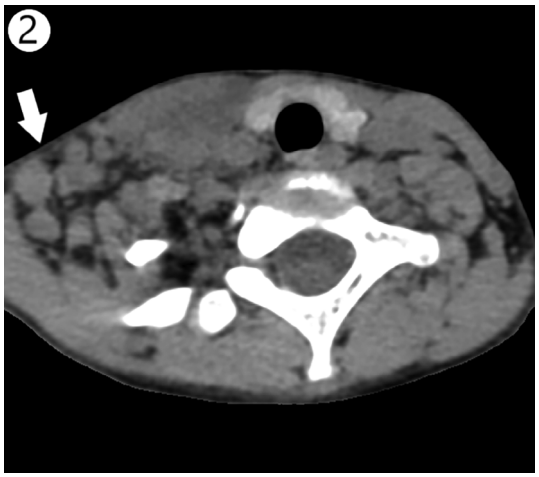

FIGURE 2 CT scan shows round, and well-circumscribed nodules in the neck.

TABLE 3 Radiological examinations of the cases.

	No. of patients (%)
All patients ($n = 134$)	
Site, *n*	
Bilateral	86 (64.2)
Right	22 (16.4)
Left	26 (19.4)
Maximum diameters, cm	
1–2	71 (53.0)
2–3	36 (26.9)
3–4	27 (20.1)

Abbreviation: cm, centimeter.

3.3 | Radiological examination

The imaging studies of the patients including ultrasound imaging, CT evaluation, MRI, or PET-CT scan were collected for analysis (Figure 2). Table 3 summarizes the imaging findings of the study subjects. A majority (65.7%) of the 134 patients presented with bilateral nodal involvement, but most patients with bilateral involvement had anasymmetrical distribution. Some patients had lymph node involvement of various body sites other than neck. The majority of our cohort had maximum lymph node sizes of 1–2 cm.

4 | DISCUSSION

KFD has been reported worldwide but the incidence is the highest in Asia. To the best of our knowledge, the present study of 134 cases is the largest clinical study of KFD in Asian countries. Our study shows that a female patient under the age of 30, presenting with cervical lymphadenopathy, fever, leukopenia, and elevated LDH should be suspected for KFD and histopathological evaluation should not be delayed.

KFD is an uncommon cause of cervical lymphadenopathy. Early series noted a striking female preponderance with a male to female ratio of 1:3–4[4,5]; however, more recent reports show only a slight female preponderance ranging from 1:1.1 to 1:2.75.[6] Our current series showed a ratio of only 1:1.73. The majority of patients in previous studies were younger than 30 years, with a mean of 25.5–30.0 years.[7,8] Patients in our study ranged in age from 4 years old to 64 years old, with a mean age of 24.9 years. KFD usually appears as posterior cervical lymphadenopathy, with unilateral lymphadenopathy accounting for 88.5%.[9] It was interesting to note that our results identified bilateral lymph node involvement to be more common, apparently.

Apart from lymphadenopathy, 30%–50% patients with KFD may have fever, usually low-grade, with upper respiratory symptoms.[10] A few patients present with atypical symptoms, weight loss, nausea, vomiting, sore throat and night sweats.[11] Approximately 16%–30% of KFD cases present with skin rashes, which may appear on the scalp, face, chest, back, and limbs.[12–14] Arthralgia occurs in approximately 7% of patients with KFD.[15] In our study, 15.7% and 6.0% of patients reported symptoms of rash and arthralgia, respectively, complicating the differentiation between KFD and SLE. KFD can also affect the nervous system, including meninges, brain parenchymal and peripheral neuropathy. One of the patients in our study had meningitis.

Currently, there are no definite laboratory tests for the diagnosis of KFD, but negative tests are important to exclude other diseases.[3] Blood work most commonly demonstrates a mild leukopenia and elevated ESR, as well as elevated LDH. Anemia and abnormal liver enzymes may also be discovered. The majority of patients' liver enzymes returned to normal values within 1 month.[15] Atypical lymphocytes may be seen on the peripheral blood smear.[16] As a hematologic malignancy must be considered, the definite diagnosis of KFD is made by histologic examination of a lymph node. A previous study indicated that approximately 15% of KFD patients had weakly positive ANA titers.[15] In our study, we found positive ANA titers in 38.2% of patients. One possible explanation for this disparity was that in our study, only a subset of the included patients was tested for ANA. As an acute-phase protein, elevated serum ferritin levels are common in infectious diseases and non-infectious inflammatory states. We reported the detection of elevated ferritin levels in 24.8% patients.

Radiologic studies with ultrasound, CT scan, MRI, or PET-CT are also not diagnostic of Kikuchi's disease but may provide a clue to the diagnosis. The lymph node appears as a round or oval hypoechoic area on ultrasound, with hilum structures visible. Lymph nodes that have hyperechoic rims are valuable for distinguishing KFD from other diseases.[17] The common CT findings in KFD included perinodal infiltration and nodal necrosis.[18] A previous study showed that the pattern of nodal necrosis and indistinct margins of necrotic foci of KFD, can be distinguished from tuberculous lymphadenopathy.[19] Perinodal infiltration can be observed in other lymphadenopathy, including lymphoma and metastasis; however, it is characteristic of inflammatory diseases.[18] The lymph nodes in KFD usually show a pattern of multiple, small, slightly enlarged, clustered nodes. By contrast, lymphoma often produces fewer, larger lymph nodes.[20] Lymph nodes usually

measure less than 4 cm and rarely reach 5 and 6 cm in diameter, but sizes reaches more than 6 cm have also been reported.[21] Our results were consistent with this. This finding could be used differentiate the diagnostic of KFD from lymphoma, especially when the affected lymph nodes do not exhibit perinodal infiltration. Turner et al. reported on 30 cases of KFD, 40% of which were initially diagnosed histopathologically as lymphoma. Some of these patients received chemotherapy or radiotherapy for their presumed malignancy.[22] The significance of MRI for the diagnosis of KFD is yet to be determined. Some studies had reported that KFD should be considered when T2-weighted images show hypointensity areas at the peripheries of enlarged cervical nodes. KFD lymph nodes have a high fluorodeoxyglucose (FDG) uptake on PET-CT. PET-CT is superior to ultrasound, CT and MRI in detecting small lymph node involvement.[23]

The correlation between KFD and SLE has been the focus of some studies in recent years. Similar clinical and histologic features were found in both disorders. SLE developed in 3 of 102 (2.9%) KFD patients in a Korean study.[24] Similar results (3.7%) were observed in our study. This was significantly higher than the general population's incidence of SLE (1–25 per 100,000).[25] A study from 2016 found the diagnosis of KFD could precede, postdate, or coincide with the diagnosis of SLE.[26] Regarding histopathology, necrosis in SLE is more extensive than that in KFD, and the necrotic area may contained a large number of plasma cells and hematoxylin bodies, forming clusters toward the edge of the area.[27] However, SLE may be morphologically indistinguishable from KFD in some cases: some SLE lymph nodes may contain very few plasma cells with or without hematoxylin bodies.[28] Thus, microscopic characteristics alone may lead to uncertain diagnoses, hence necessitating lab testing including ANA, and effective communication between the otolaryngologist and pathologist for accurate diagnosis of KFD.

In some of our patients, lymphadenopathy resolved or improved spontaneously within 1–4 months without treatment. Current treatments are primarily supportive and aim to help ameliorate persistent fever and pain. In patients with extensive nodal involvement or sever clinical signs, short-term corticosteroid therapy is the treatment of choice, though immunosuppressants may also be considered.[29]

This study is a retrospective case series including a relatively large cohort of 134 patients. Several points should be considered limitations of our study. Firstly, only some of the included patients were tested for ANA and ferritin, which may bias some conclusions. Secondly, this study only included clinical data, and no histopathology data were included. Lastly, all data are derived from one hospital and the findings may not be generalizable to other settings.

5 | CONCLUSION

Overall, KFD should be a considered diagnosis in a female patient under the age of 30, presenting with cervical lymphadenopathy, fever, leukopenia, and elevated LDH. Accurate identification of KFD is necessary in order to prevent unwarranted diagnostic procedures and inappropriate treatments. Given the marked predilection of this disease for cervical lymph nodes, the otolaryngologist will play an important role in the diagnosis of KFD.

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CONFLICT OF INTEREST STATEMENT

The authors declares that they has no conflict of interest.

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