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Symptom-based Kikuchi disease subtypes: Clinical scenarios across specialties in Taiwan with temporal trends analysis

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ABSTRACT

Background: We propose a subtyping system for Kikuchi disease based on chief complaints and fever status.
Methods: A chart review of 388 patients diagnosed with Kikuchi disease.
Results: The subtypes afebrile lymphadenopathy (aLAP), febrile lymphadenopathy (FebLAP), and febrile accounted for 68 %, 18 %, and 14 % of cases, respectively. aLAP patients were older (median 26 years), predominantly female, had fewer laboratory abnormalities, and a lower recurrence rate (5 %). In contrast, the febrile type included younger patients (median 17 years), predominantly male, with more laboratory abnormalities and a higher recurrence rate (20 %). FebLAP exhibited intermediate characteristics. Otolaryngology had the highest number of patients (272, 70 %), mainly with aLAP, typically diagnosed via outpatient needle biopsy, with a short follow-up duration. Infectious disease specialists (adult and pediatric) managed 67 patients (17 %), often encountering the febrile type, with patients frequently seen in the emergency room or hospitalized, diagnosed via surgical biopsy, and followed up more intensively and over longer periods. Approximately 9 % of patients were referred to rheumatology; these patients more frequently used disease-modifying antirheumatic drugs and steroids and were followed for an extended duration. From 2005 to 2022, the incidence of Kikuchi disease has doubled, driven by otolaryngologists' aggressive use of ultrasound-guided core needle biopsy to diagnose more aLAP cases.
Conclusions: Patients of different subtypes exhibit distinct characteristics, including demographic and laboratory data, recurrence rates, medical-seeking behaviors, diagnostic methods, treatments, and follow-up approaches, underscoring the clinical significance of this subtyping system. Changes in biopsy methods have led to the diagnosis of more aLAP cases.

1. Introduction

Kikuchi disease (Kikuchi-Fujimoto disease) is a form of benign lymphadenopathy.[1–3]. It is believed to involve immune responses[4–7] triggered by infections,[8] vaccines,[9,10] and other factors in genetically predisposed individuals.[11,12]. Numerous studies have strongly associated it with autoimmune diseases.[1,3,13,14].

Clinical manifestations typically include fever and cervical lymphadenopathy, along with nonspecific symptoms such as fatigue.[1–3,15–18]. Common laboratory findings include abnormal blood cell counts, elevated erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH), C-reactive protein (CRP), liver enzymes, and positive anti-nuclear antibodies (ANA).[1–3,15–19].

The diagnosis relies on histopathological examination. This examination reveals necrotizing lymphadenitis characterized by karyorrhexis, increased plasmacytoid dendritic cells, and myeloperoxidase-positive macrophages.[3,20–23].

Kikuchi disease is typically self-limiting, often resolving spontaneously within months.[1–3]. Apart from observation, various treatment methods have been reported, including steroids, non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, antibiotics, hydroxychloroquine, etc., either as monotherapy or in combination.[1,2].

Recurrence occurs in a subset of patients,[1–3,14–19,24,25] with timing varying from months to years.[3,14–16,18,19]. The differences in recurrence rate and timing may be due to the lack of a consensus definition for recurrence. Efforts to identify risk factors for recurrence have yielded

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inconsistent results without established criteria for patient stratification.[14,16,19,24,25].

Currently, the histological subtyping categorizes Kikuchi disease into proliferative, necrotizing, and xanthomatous types.[3,20,26]. However, its clinical significance lacks empirical validation.[3,5,26].

This study introduces a practical subtyping approach based on clinical presentations—specifically, fever and neck mass—to classify patients into three distinct groups: febrile, febrile lymphadenopathy (FebLAP), and afebrile lymphadenopathy (aLAP). This classification aims to differentiate patient groups with unique medical-seeking behaviors and diagnostic pathways, reflecting common clinical scenarios in Kikuchi disease. To validate this approach, we analyzed clinical data from 388 Kikuchi disease patients.

2. Methods

2.1. Patients

We searched the surgical pathology archives for neck lymph node specimens of Kikuchi disease diagnosed from 2005 to 2022. Patients with systemic lupus erythematosus were excluded as cases mimicking Kikuchi disease.[3,26–28].

2.2. Pathological review

Histopathological slides were reviewed to confirm the Kikuchi disease diagnosis. C4d immunohistochemical staining results were extracted from the pathological reports.[27].

2.3. Clinical history

We reviewed medical records before December 2023 for age at the time of biopsy, sex, chief complaint, and fever status. We documented medical encounters, including the department visited, biopsy method, medications, follow-up interval and duration.

Lymphadenopathy before or after the diagnosis of Kikuchi disease, with an interval exceeding one year, was recorded as previous or recurrent lymphadenopathy. Regarding recurrence, we did not consider biopsy results, as false negatives due to sampling errors are inevitable,[29] and some patients clinically suspected of Kikuchi disease recurrence do not undergo a second biopsy. Lymphadenopathy caused by specific etiologies, such as malignancy or tuberculosis, was not classified as recurrent lymphadenopathy. However, conditions like viral infections or autoimmune diseases, which are known to be associated with Kikuchi disease,[1,3,8–10,13,14,30] were included as recurrent lymphadenopathy. Although this definition may not perfectly capture Kikuchi disease recurrence, we use it as a surrogate indicator with clear criteria.

2.4. Laboratory data

Hemogram data were reviewed for anemia, thrombocytopenia, neutropenia, and lymphopenia based on age- and gender-specific normal ranges.[31]. Some of the clinical and hemogram data were previously reported in our earlier studies.[27,31]. Other laboratory data reviewed included CRP, LDH, ESR, liver enzymes, albumin, total bilirubin, renal function, coagulation profiles, autoantibodies, complement C3 and C4, and viral serology.

2.5. Symptom-based subtyping

Patients were categorized by chief complaint and fever status (Fig. S1). Patients with fever as the chief complaint were classified as the febrile type. It is important to note that patients in the febrile type must also present with lymphadenopathy, even if it is not the chief complaint. Patients with a chief complaint of neck mass were further classified as FebLAP if fever was present and as aLAP if fever was absent. The presence or absence of fever was determined based on medical records, not measured body temperature.

2.6. Statistical analysis

Categorical data were analyzed using Fisher's exact test and chi-square test; continuous data were compared using the Kruskal – Wallis test. A two-tailed P-value <0.05 was considered statistically significant. Statistical analyses were performed using the R language (version 4.4.1; R Foundation, Vienna, Austria).

3. Results

3.1. Overview of patient profiles

The average age of the 388 patients was 26 years, with 244 females and 144 males. Table S1 summarizes the laboratory data, including the results and availability rates. 34 patients (9 %) developed recurrent lymphadenopathy, with a median recurrence time of 4 years.

316 (81 %) visited the outpatient department (OPD); 54 of them were hospitalized. 68 (18 %) visited the emergency room (ER); 49 of them were hospitalized. 4 (1 %) were directly admitted from other hospitals. Initial departments included otolaryngology (70 %), pediatric infectious diseases (9 %), infectious diseases (8 %), and hematology (5 %). 204 patients (53 %) were diagnosed via needle biopsy, and 184 (47 %) via surgical biopsy.

Most patients did not receive medication after diagnosis. Common medications included acetaminophen (17 %), NSAIDs (16 %), steroids (12 %), antibiotics (10 %), and disease-modifying antirheumatic drugs (DMARDs) (3 %). DMARDs included hydroxychloroquine (11 patients), azathioprine (1 patient), and sulfasalazine (1 patient). The median follow-up after biopsy was only 17 days; 200 (52 %) patients did not follow up after diagnosis.

This single-center, large-scale case series provides detailed data on Kikuchi disease, highlighting patient characteristics, medical-seeking behaviors, diagnostic pathways, and follow-up approaches.

3.2. Symptom-based subtypes

Patients were divided into three subtypes based on chief complaint and fever status (Fig. S1). Of the 388 patients, 264 (68 %) were classified as aLAP, 68 (18 %) as FebLAP, and 56 (14 %) as febrile.

Demographic and laboratory data of patients differed significantly among the three subtypes (Table 1). Patients with aLAP tended to be older (median 26 years) and predominantly female, while febrile subtype patients were younger and predominantly male, exhibiting a right-skewed age distribution (mean 20 years, median 17 years). Febrile subtype patients exhibited more laboratory abnormalities (Table 1). FebLAP was intermediate between aLAP and febrile, exhibiting characteristics of both extremes.

Recurrent lymphadenopathy rates were highest in the febrile subtype (20 %), followed by FebLAP (13 %) and lowest in aLAP (5 %; Table 1). However, the time to recurrence did not differ among the subtypes.

Recent cases may underestimate the recurrence of lymphadenopathy. We separately analyzed cases from 2005 to 2016, showing significant differences in recurrence rates among subtypes: febrile 26 % (8/31), FebLAP 21 % (8/39), and aLAP 8 % (12/152; $P = 0.006$). Time to recurrence also did not differ significantly among the subtypes, nor did it exceed that of the entire cohort.

Additionally, a majority of recurrent lymphadenopathy in the febrile subtype was accompanied by fever, higher than in the other two subtypes (Table 1). However, this difference was not statistically significant.

Medical care-seeking behavior and diagnostic pathways varied between subtypes. aLAP patients primarily sought care at otolaryngology (Fig. 1A) OPD (Fig. 1B and Fig. S2) and were often diagnosed via needle

Table 1
Patient characteristic across subtypes.

	aLAP	FebLAP	Febrile	*P*-value
Case number	264 (68 %)	68 (18 %)	56 (14 %)	
Age, year				<0.001
Mean ± SD	27 ± 9	25 ± 11	20 ± 11	
Median (Q3, Q1)	26 (21, 33)	24 (18, 31)	17 (10, 30)	
Sex				0.003
Female	177 (67 %)	43 (63 %)	24 (43 %)	
Male	87 (33 %)	25 (37 %)	32 (57 %)	
CBC data available	196 (74 %)	62 (91 %)	53 (95 %)	<0.001
Anemia	29 (15 %)	16 (26 %)	24 (45 %)	<0.001
Thrombocytopenia	12 (6 %)	4 (6 %)	12 (23 %)	0.002
Neutropenia	24 (12 %)	6 (10 %)	17 (32 %)	0.002
Lymphopenia	18 (9 %)	16 (26 %)	30 (57 %)	<0.001
Atypical lymphocytes	14 (7 %)	6 (10 %)	7 (13 %)	0.318
CRP data available	89 (34 %)	45 (66 %)	50 (89 %)	<0.001
CRP, mg/dL	0.64 ± 2.61	2.08 ± 2.66	2.30 ± 3.41	<0.001
LDH data available	175 (66 %)	51 (75 %)	53 (95 %)	<0.001
LDH, U/L	255 ± 154	376 ± 360	600 ± 423	<0.001
AST data available	74 (28 %)	33 (49 %)	46 (82 %)	<0.001
AST, U/L	28 ± 15	29 ± 22	56 ± 92	0.001
ALT data available	86 (33 %)	44 (65 %)	51 (91 %)	<0.001
ALT, U/L	23 ± 17	28 ± 27	58 ± 121	0.050
ESR data available	22 (8 %)	16 (24 %)	28 (50 %)	<0.001
ESR, mm/hour	20 ± 14	34 ± 21	34 ± 27	0.080
ANA data available	33 (13 %)	29 (43 %)	41 (73 %)	<0.001
ANA positive	2 (7 %)	3 (10 %)	8 (20 %)	0.234
Recurrent lymphadenopathy	14 (5 %)	9 (13 %)	11 (20 %)	0.001
Time to recurrence, median (Q3, Q1), year	5 (3, 7)	4 (2, 6)	4 (3, 9)	0.872
Accompanied with fever	2 (14 %)	1 (11 %)	6 (55 %)	0.054
Past history of lymphadenopathy	14 (5 %)	5 (7 %)	0 (0 %)	0.135
Accompanied with fever	0 (0 %)	2 (40 %)	NA	0.059

CBC, complete blood counts; NA, not applicable; Q1, 25 % quartile; Q3, 75 % quartile; SD, standard deviation.

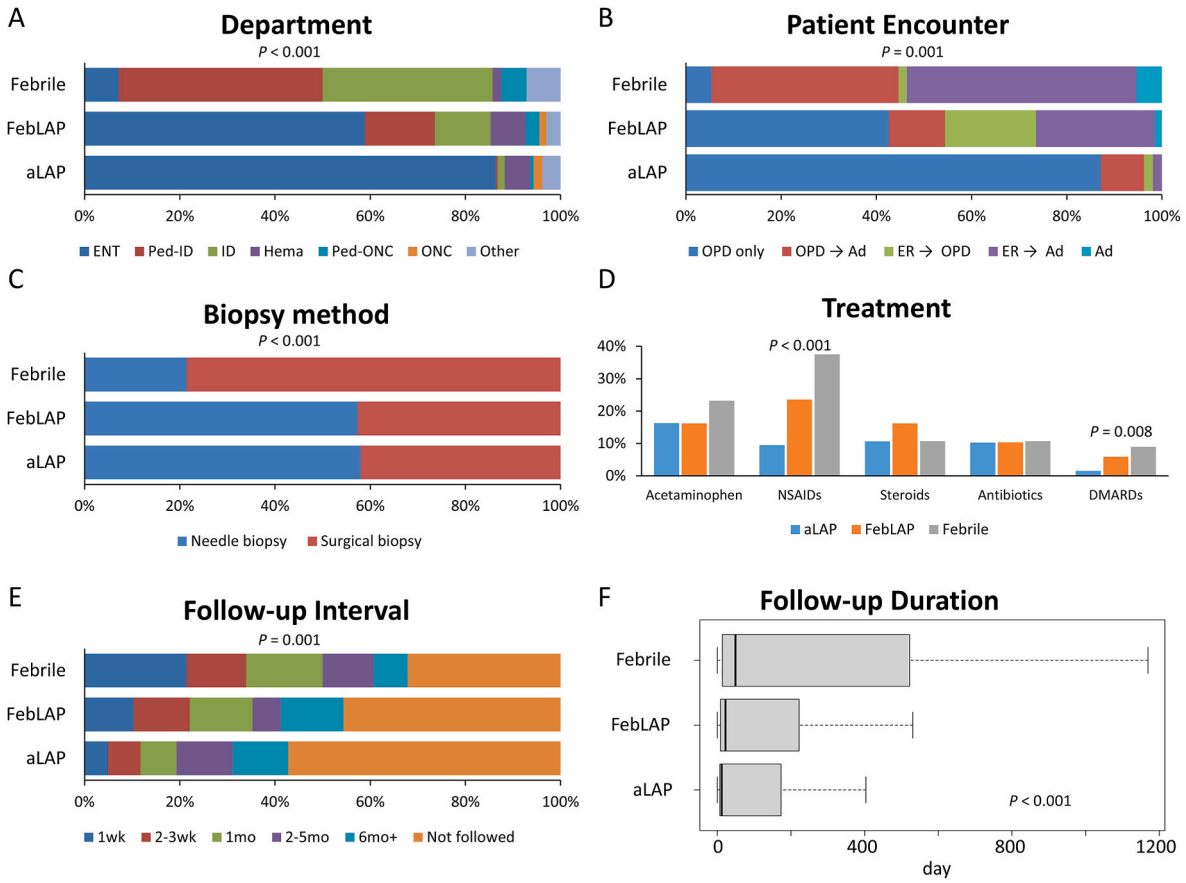

Fig. 1. Medical-seeking behavior, and diagnostic, therapeutic and follow-up approaches across subtypes. (A) Department (B) Patient encounter (C) Biopsy method (D) Treatment (E) Follow-up interval (F) Follow-up duration
Abbreviations: Ad, admission; ENT, otolaryngology; ER, emergency room; Hema, hematology; ID, infectious diseases; mo, month; ONC, medical oncology; OPD, outpatient department; Ped-ID, pediatric infectious diseases; Ped-ONC, pediatric hematology and oncology; wk, week.

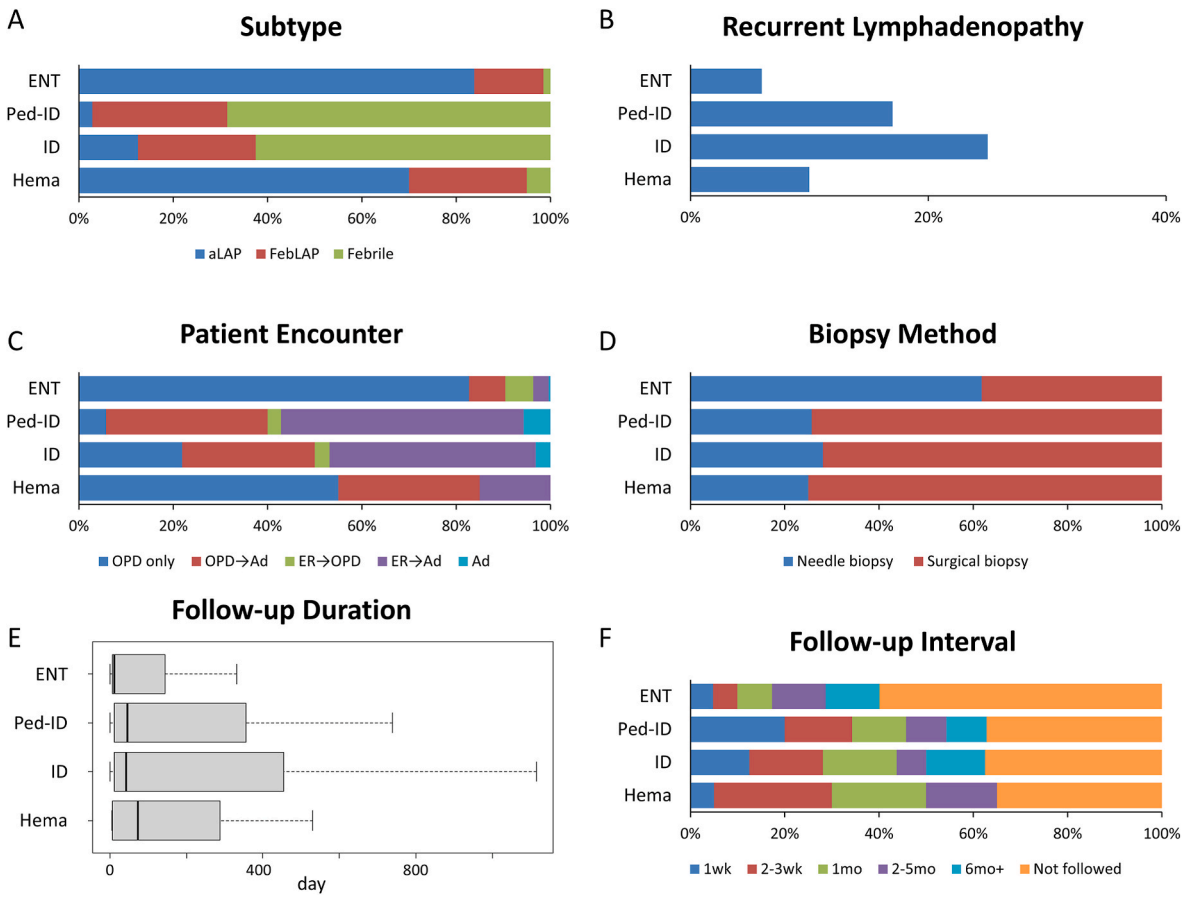

Fig. 2. Comparison between otolaryngology (ENT), pediatric infectious disease (Ped-ID), infectious disease (ID), and hematology (Hema) patients. (A) Subtype (B) Frequency of recurrent lymphadenopathy (C) Patient encounter (D) Biopsy method (E) Follow-up duration (F) Follow-up interval
Abbreviations: Ad, admission; ER, emergency room; mo, month; OPD, outpatient department; wk, week.

biopsy (Fig. 1C). In contrast, febrile subtype patients typically consulted infectious disease specialists (Fig. 1A), or visited the ER, leading to frequent hospitalizations (Fig. 1B and Fig. S2) and diagnoses often made via surgical biopsy (Fig. 1C). FebLAP patients exhibited intermediate characteristics; their ER visit rate was high, similar to the febrile subtype, but the hospitalization rate from the ER was lower. More FebLAP patients were referred from the ER to OPD (Fig. 1B and Fig. S2) and subsequently diagnosed via needle biopsy (Fig. 1C).

Treatment varied among the subtypes: febrile type patients most frequently receiving NSAIDs and DMARDs (38 % and 9 %, respectively), while aLAP patients were least likely to receive these treatments (NSAIDs 9 %, DMARDs 2 %; Fig. 1D). There was no difference in the use of acetaminophen, steroids, or antibiotics (Fig. 1D).

Follow-up varied between subtypes. Most aLAP patients did not follow up after diagnosis; if they did, the interval was usually more than two months (Fig. 1E). In contrast, the follow-up interval for febrile patients was significantly shorter, typically ranging from one week to one month (Fig. 1E). The median follow-up duration after biopsy was longest for febrile patients (50 days), followed by FebLAP patients (22 days), and shortest for aLAP patients (12 days; Fig. 1F).

Overall, data regarding follow-up duration and recurrence indicate that only 18 % (6/34) of recurrences were identified during outpatient follow-up, while the remaining 82 % (28/34) were discovered by patients who had discontinued follow-up and returned to the clinic after self-discovering lymphadenopathy. The recurrence rates identified during outpatient follow-up for the three types were: Febrile 7 % (4/56), FebLAP 1 % (1/68), and aLAP 0 % (1/264). Similarly, the recurrence rates for those self-discovered were: Febrile type 13 % (7/56), FebLAP 12 % (8/68), and aLAP 5 % (13/264). This suggests that regardless of follow-up duration, the recurrence rates align with the trend of Febrile > FebLAP > aLAP. Thus, the high recurrence rate in the Febrile type is not solely attributable to a longer follow-up duration.

In summary, the subtypes present distinct clinical scenarios. We can infer that specialists from various departments may encounter different subtypes of Kikuchi disease, influencing their perception and management of the disease.

3.3. *Patients across specialties*

To support the above inference, we analyzed patients across specialties. We selected the four departments with ≥20 patients (accounting for 92 % of patients) to illustrate in Fig. 2.

Otolaryngology and hematology patients were predominantly aLAP (Fig. 2A and Table S2), whereas pediatric infectious disease and infectious disease patients were mainly febrile (Fig. 2A and Table S2).

Pediatric patients had a higher male proportion (Table S2). We and other groups have previously reported this male predominance in children.[25,31].

Recurrent lymphadenopathy was most common in infectious disease departments and least in otolaryngology (Fig. 2B and Table S2), consistent with the distribution of subtypes.

Pediatric infectious disease and infectious disease patients had a higher percentage of cytopenia and elevated levels of CRP and LDH (Table S3), also consistent with the distribution of subtypes.

Patients exhibited varying medical-seeking behaviors and diagnostic pathways across departments. Most otolaryngology patients were treated as outpatients, while most hematology patients also came from the OPD but a significant proportion were later hospitalized (Fig. 2C,

Table 2
Patients with and without rheumatology referrals.

	Referred	Not referred	*P*-value
Case number	34 (9 %)	354 (91 %)	
Subtype			0.001
aLAP	15 (44 %)	249 (70 %)	
FebLAP	7 (21 %)	61 (17 %)	
Febrile	12 (35 %)	44 (12 %)	
Recurrent lymphadenopathy	4 (12 %)	30 (8 %)	0.522
ANA positive	6/29 (20 %)	7/74 (9 %)	0.184
C4d endothelial staining	3/14 (21 %)	19/72 (26 %)	0.547
Department			0.024
Otolaryngology	19 (56 %)	253 (71 %)	
Pediatric infectious diseases	4 (12 %)	31 (9 %)	
Infectious diseases	5 (15 %)	27 (8 %)	
Hematology	0 (0 %)	20 (6 %)	
Pediatric hematology and oncology	2 (6 %)	5 (1 %)	
Medical oncology	0 (0 %)	6 (2 %)	
Other departments	4 (12 %)	12 (3 %)	
Patient encounter			0.171
OPD only	18 (53 %)	244 (69 %)	
OPD → Ad	6 (18 %)	48 (14 %)	
ER → Ad	7 (21 %)	42 (12 %)	
ER → OPD	2 (6 %)	17 (5 %)	
Ad	1 (3 %)	3 (1 %)	
Treatment			
Acetaminophen	3 (9 %)	64 (18 %)	0.236
NSAIDs	8 (24 %)	54 (15 %)	0.221
Steroids	8 (24 %)	37 (10 %)	0.043
Antibiotics	1 (3 %)	39 (11 %)	0.233
DMARDs	11 (32 %)	2 (1 %)	<0.001
Follow-up duration, median (Q3, Q1), day	283 (58, 1024)	13 (7, 175)	<0.001
Follow-up interval			<0.001
1 week	6 (18 %)	26 (7 %)	
2–3 weeks	12 (35 %)	21 (6 %)	
1 month	5 (15 %)	33 (9 %)	
2–5 months	4 (12 %)	37 (10 %)	
6 months or longer	3 (9 %)	41 (12 %)	
Not followed	4 (12 %)	196 (55 %)	

Ad, admission; ER, emergency room; OPD, outpatient department; Q1, 25 % quartile; Q3, 75 % quartile.

Fig. S3 and Table S4). The majority of pediatric infectious diseases and infectious diseases patients were hospitalized, primarily coming through the ER (Fig. 2C, Fig. S3 and Table S4). The rate of needle biopsies was particularly high in the otolaryngology department (Fig. 2D and Table S4).

Treatment differences among departments correspond to the subtypes. Infectious disease patients received NSAIDs more frequently than those in otolaryngology and hematology (Table S5). The proportion of patients using DMARDs was highest in infectious disease, followed by hematology and pediatric infectious disease, with otolaryngology being the lowest (Table S5). Hematologists most frequently used steroids, presenting a different pattern compared to other specialties that primarily used acetaminophen and NSAIDs (Table S5).

The follow-up approach also varied across specialties. Median follow-up duration was shortest in otolaryngology (12 days) and longest in hematology (74 days; Fig. 2E and Table S5), with most otolaryngology patients not following up (Fig. 2F and Table S5). In contrast, other departments followed up with patients more frequently, many with intervals of weeks, whereas otolaryngology patients were rarely followed up this frequently (Fig. 2F and Table S5).

These findings show that otolaryngologists and infectious disease specialists encounter diverse patient subtypes. Consequently, patient characteristics differ, influencing their diagnostic, therapeutic, and follow-up approaches. Hematologists encounter patient subtypes similar to those seen by otolaryngologists, but they hospitalize patients more frequently, use needle biopsies less often, and have longer follow-up durations.

Table 3
Additional data of patients with rheumatology referrals.

Symptoms	N (%)
Skin rash	8 (24 %)
Dry mouth	8 (24 %)
Dry eyes	7 (21 %)
Oral ulcer	4 (12 %)
Arthralgia	4 (12 %)
Photosensitivity	1 (3 %)
Autoimmune diseases	**N (%)**
Sjögren syndrome	2 (6 %)
Autoimmune thyroiditis	1 (3 %)
Antiphospholipid syndrome	1 (3 %)
Laboratory abnormalities	**Positive/Available (%)**
ANA	6/29 (21 %)
1:80	2/29 (7 %)
1:160	2/29 (7 %)
1:320	2/29 (7 %)
Anti-dsDNA antibody	0/20 (0 %)
Anti-ENA antibody	0/16 (0 %)
Anti-Sm antibody	1/10 (10 %)
Anti-SSA antibody	1/17 (6 %)
Anti-SSB antibody	0/17 (0 %)
Rheumatoid factor	0/19 (0 %)
Anti-cardiolipin antibody, IgG	0/13 (0 %)
Anti-cardiolipin antibody, IgM	0/12 (0 %)
Anti-beta-2-glycoprotein antibody	0/8 (8 %)
Anti-MPO antibody	0/5 (0 %)
Anti-PR3 antibody	0/5 (0 %)
Low C4	0/30 (0 %)
Low C3	0/29 (0 %)
Elevated ESR	20/30 (67 %)
Treatment	**N (%)**
DMARDs alone	5 (15 %)
Steroids alone	4 (12 %)
NSAIDs alone	2 (6 %)
Acetaminophen alone	1 (3 %)
DMARDs + Steroids	2 (6 %)
DMARDs + NSAIDs	3 (9 %)
DMARDs + Steroids + NSAIDs	1 (3 %)
Steroids + NSAIDs + Acetaminophen	1 (3 %)
NSAIDs + Antibiotics	1 (3 %)
No above medication	14 (41 %)

3.4. Rheumatology referrals

Only 34 (9 %) patients were referred to rheumatology after diagnosis. We first compared patients with and without referrals, selecting a subset of parameters summarized in Table 2. These patients had a lower proportion of aLAP subtypes than non-referred patients. Infectious disease specialists were more likely to refer patients, while hematologists made no referrals. Referred patients had a slightly higher hospitalization rate, but it was not statistically significant.

Referred patients had no significant differences in demographics or ANA positivity compared to non-referred patients (Table 2). Referred patients had slightly lower C4 (29 ± 13 mg/dL vs. 36 ± 21 mg/dL, $P = 0.016$) and creatinine levels (0.6 ± 0.2 mg/dL vs. 0.8 ± 0.4 mg/dL, $P = 0.014$). This indicates that previously reported autoimmune-related risk factors do not determine referral.[1,13,14,27].

A notable difference was observed in treatment and follow-up patterns (Table 2). Referred patients were more likely to receive DMARDs and steroids than non-referred patients. Referred patients had a significantly longer follow-up period. Only 12 % of referred patients did not follow up, versus 55 % of non-referred patients. The most common follow-up interval for referred patients was 2–3 weeks, whereas for non-referred patients, it was over 6 months and 2–5 months.

Reviewing the 34 referred patients (Table 3), we found detailed symptom records, with common symptoms including skin rash, dry mouth, and dry eyes. They underwent more laboratory tests, with

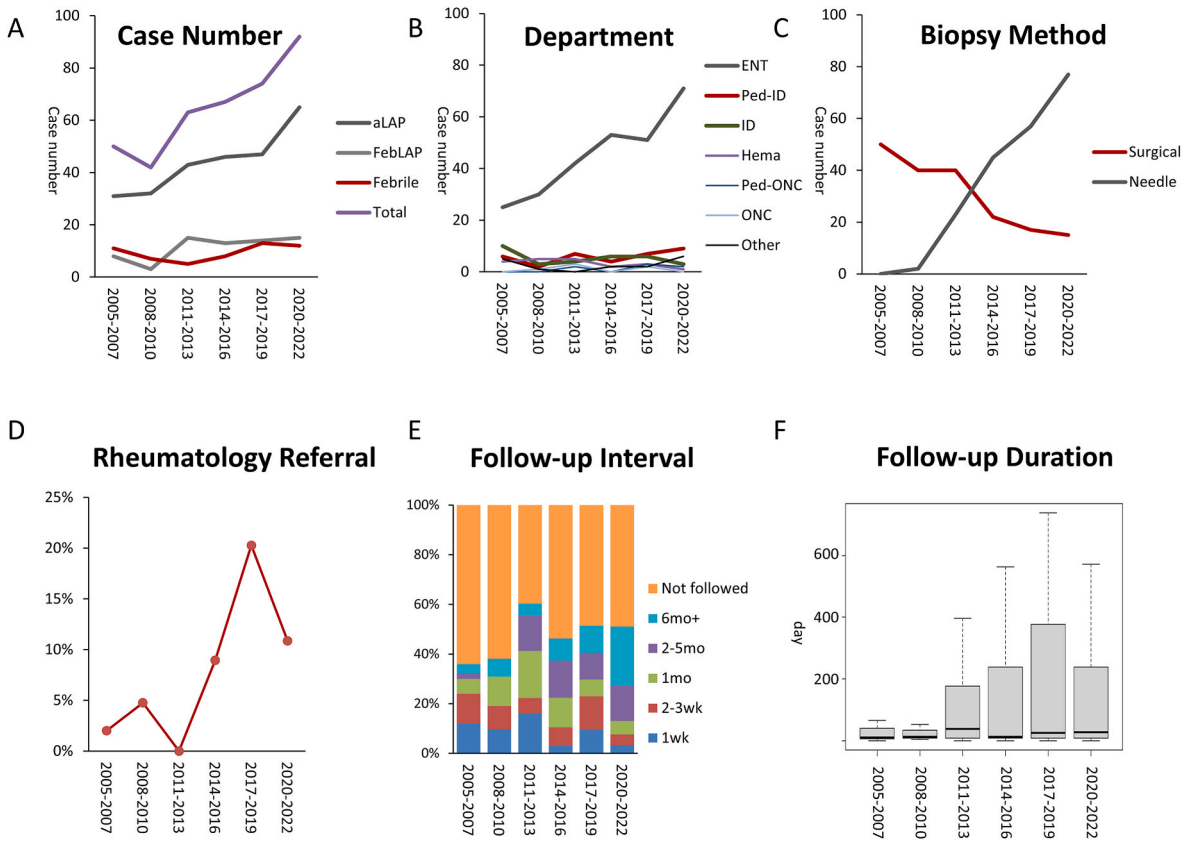

Fig. 3. Temporal trend analysis. (A) Case number, total and subtypes (B) Department (C) Biopsy method (D) Rate of rheumatology referral (E) Follow-up interval (F) Follow-up duration

Abbreviations: ENT, otolaryngology; Hema, hematology; ID, infectious diseases; mo, month; ONC, medical oncology; Ped-ID, pediatric infectious diseases; Ped-ONC, pediatric hematology and oncology; wk, week.

elevated ESR being relatively common, although other abnormalities were infrequent.

Among the 34 patients, DMARDs alone (5 patients) and steroids alone (4 patients) were most common treatments (Table 3). However, 14 of the 34 patients did not receive any treatment with DMARDs, steroids, NSAIDs, acetaminophen, or antibiotics (Table 3).

Three patients had associated autoimmune disease similar to those in other studies (Table 3).[13,14,30]. One of them had both antiphospholipid syndrome and autoimmune thyroiditis. Two of the three patients were classified as febrile type, suggesting a potential association with a higher risk of the febrile subtype, although statistical significance was not observed.

The referral rate after lymphadenopathy recurrence was also 9 % (3/34), similar to the initial diagnosis.

3.5. *Temporal trends analysis*

We analyzed the temporal trends of the data. First, we observed that there has been a gradual increase in Kikuchi disease cases, with recent incidence rates approximately double those of earlier years (Fig. 3A). This increase is mainly due to the rise in the aLAP subtype, while the other two subtypes have remained stable (Fig. 3A).

Otolaryngology saw a dramatic increase, with recent cases tripling earlier numbers (Fig. 3B). Needle biopsy sporadically began in 2008 and rapidly increased, while surgical biopsies have significantly decreased to less than half of earlier numbers (Fig. 3C).

The increased cases are likely due to otolaryngologists using ultrasound-guided core needle biopsy more aggressively,[29,32] leading to more aLAP diagnoses.

There have also been changes in post-diagnosis management. The first change is in the rheumatology referral rate. Earlier, Kikuchi disease patients were rarely referred to rheumatology, but referrals increased after 2014 (Fig. 3D). The second change is in treatment. The use of acetaminophen and antibiotics has gradually decreased (Fig. S4), which may be related to the decreasing proportion of febrile and FebLAP types over time. Another change is in the follow-up pattern. In earlier years, the follow-up approach was extreme; most patients were not followed up, but those who were had very frequent follow-ups, with intervals of only a few weeks. Recently, the proportion of patients not followed up has decreased, with follow-up intervals now typically several months (Fig. 3E). This follow-up approach may have reduced the loss of follow-up. Follow-up duration was short in earlier years but began lengthening after 2011 (Fig. 3F).

4. Discussion

We proposed a new subtyping for Kikuchi disease to clarify clinical profiles and patient management across specialties. This subtyping is based on pathologists' observations. Despite identical microscopic findings, we observed significant differences in otolaryngology and infectious disease patients, resulting in distinct diagnostic, therapeutic, and follow-up approaches. These differences justify stratifying patients into subtypes: aLAP for otolaryngology and febrile for infectious disease.

The proposed subtypes— aLAP, FebLAP, and febrile—show distinct demographics, laboratory findings, and recurrence rates. aLAP typically involves young female adults with few laboratory abnormalities and a low recurrence rate. The febrile subtype includes atypical demographic data, common laboratory abnormalities, and a high recurrence rate. The febrile subtype characteristics closely align with previously identified recurrence risk factors.[14,16,19,24,25].

Traditional Kikuchi disease characteristics reflect a hybrid of subtypes. Demographics like young females[1–3] reflect aLAP characteristics, while laboratory abnormalities[1–3,15–19] are more common in febrile patients. Combined characteristics are rare, making subtyping more precise.

Due to differences in patient characteristics, medical care-seeking behavior and healthcare providers' practices vary. aLAP patients are often diagnosed via outpatient needle biopsy, usually without follow-up. Febrile patients more often present in emergency settings, typically diagnosed via surgical biopsy. They are more likely to receive NSAIDs and DMARDs, with higher follow-up frequency and duration.

Analysis shows otolaryngologists and infectious disease specialists encounter aLAP and febrile patients, respectively, leading to diverse diagnostic and management strategies. aLAP predominates, significantly outnumbering the other two subtypes. Otolaryngologists, experienced with aLAP cases, favor needle biopsy and are confident in their diagnostics. Infectious disease specialists manage the rarer febrile type, which has more frequent laboratory abnormalities, requiring a cautious management approach.

Hematologists, although encountering similar patient subtypes as otolaryngologists, exhibit distinct management practices. They have higher hospitalization rates, less frequent needle biopsy use, and longer follow-ups. These practices resemble those of infectious disease specialists, likely due to their experience with lymphoma, requiring a cautious approach to lymphadenopathy.

The referral rate of Kikuchi disease to rheumatology is 9 %, with similar rates for initial diagnosis and recurrence. Despite extensive literature on Kikuchi disease and autoimmune diseases,[1,3,13,14] most cases are not referred. Referral decisions relate to subtype and department, with cautious infectious disease specialists referring more often.

Rheumatology referrals show significant differences in post-diagnosis management, highlighting rheumatologists' crucial role in Kikuchi disease care. Referred patients more often receive DMARDs and steroids, with longer follow-ups at shorter intervals.

Referred patients have more detailed autoantibody and immune profiles than previous case series.[15–19]. Our study offers new data on these laboratory findings in Kikuchi disease.

Temporal trend analysis shows a rise in Kikuchi disease cases, driven by more aLAP diagnoses and evolving biopsy practices. Otolaryngologists using ultrasound-guided core needle biopsy[29,32] have diagnosed more aLAP cases, significantly increasing identified Kikuchi disease cases. Previously, some aLAP patients may had lymphadenopathy resolve without biopsy. Aggressive biopsy practices have led to identifying these Kikuchi disease cases. This trend reflects the significant contribution of ultrasound-guided core needle biopsy in diagnosing lymphadenopathy in recent years.

Recent changes in post-diagnosis management, including higher rheumatology referral rates and modified follow-up patterns, suggest an adaptation in clinical approaches to improve patient care. With more patients, clinicians have become familiar with the disease, recognizing autoimmune risks and referring more to rheumatology. Follow-ups are now less frequent but longer.

Limitations include its single-institution design, potentially limiting generalizability. Many patients lacked detailed medical records and complete laboratory data, possibly introducing bias. Additionally, the absence of long-term follow-up could affect the reliability of the recurrence rates.

Identifying new subtypes of Kikuchi disease enhances our understanding of its clinical diversity and allows for the development of tailored strategies for management. Future guidelines should be tailored to these distinct subtypes, reflecting their unique characteristics. Additionally, the differences among these subtypes suggest the need for further investigation into their underlying biological mechanisms. The widespread use of ultrasound-guided core needle biopsy has resulted in the diagnosis of more cases of Kikuchi disease, significantly transforming medical practice.

CRediT authorship contribution statement

Shan-Chi Yu: Writing – review & editing, Writing – original draft, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Tseng-Cheng Chen:** Writing – review & editing, Data curation. **Chun-Nan Chen:** Writing – review & editing, Data curation. **Tsung-Lin Yang:** Writing – review & editing, Data curation.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2025.02.009.

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