

Clinicopathological Study of Kimura disease and Angiolymphoid hyperplasia with eosinophilia in patients at Maharaj Nakorn Chiang Mai Hospital

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Objective To evaluate clinicopathologic differences between Kimura disease (KD) and angiolymphoid hyperplasia with eosinophilia (ALHE)

Methods Clinical data and pathological slides of KD and ALHE patients at Maharaj Nakorn Chiang Mai Hospital from 1999 through 2011 were retrieved and analyzed.

Results A total of 32 KD patients (21 males; 11 females) age 2-74 years (mean 36.44) presented with a painless mass (size 0.4-10 cm; mean 3.75) in the head and neck region had been treated during the study period. The masses had been present for between 1 and 228 months (mean 28.27). There were also 19 ALHE patients (13 males; 6 females) age 1-66 years (mean 32), most of whom had a firm, painless mass (n=14) measuring 0.2-3 cm (mean 1.09). Of the ALHE cases, one had a cystic lesion, 2 had indurated skin and 2 had nasal obstruction. Duration of symptoms in the ALHE patients ranged from 1 to 36 months (mean 8.63). Presentation with a painless mass was a significant clinical diagnostic for KD ($p = 0.005$). Differences in histologic findings between KD and ALHE included the presence of lymphoid follicles in KD ($p < 0.000$) and the extension of KD into deep subcutaneous tissue, salivary glands and skeletal muscle ($p = 0.029$).

Conclusions KD was found in female and middle-aged patients, not just young males as previously reported. Conditions which would indicate the presence of KD rather than ALHE include presentation with a mass, pathologic findings of lymphoid follicles and extension into the deep subcutaneous tissue, skeletal muscle and salivary gland. **Chiang Mai Medical Journal 2017;56(4):213-21.**

Keywords: Kimura disease, Angiolymphoid hyperplasia with eosinophilia

Introduction

Kimura disease (KD) has been known for over 70 years. In 1937 Kim and Szeto reported 7 cases in China, describing it as “eosinophilic hyperplastic lymphogranuloma” (1). The condition became widely known as Kimura disease after Kimura et al, reported similar cases in Japan under title “On unusual granulation com-

bined with hyperplastic changes in lymphoid tissues” (2).

KD has been reported to be more prevalent in young Asian males (20-30 years of age), especially Chinese and Japanese patients. It presents as a deep subcutaneous tumor-like nodule with a predilection for the head and

neck region and it is frequently associated with regional lymphadenopathy or salivary gland involvement. Epitrochlear, axillary, inguinal and popliteal localizations have been described. Laboratory analyses have detected peripheral blood eosinophilia and increased serum total IgE concentrations in KD patients. Proteinuria, which can be a sign of a nephrotic syndrome, must be systematically evaluated in Kimura patients. The histological characteristics of KD include hyperplastic lymphoid tissue with well-developed lymphoid follicles, inflammatory infiltrate rich in eosinophils, proliferation of thin-walled postcapillary venules, and varying degrees of fibrosis (3-7).

Angiolymphoid hyperplasia with eosinophilia (ALHE) was first reported by Wells and Whimster in 1969. They described the histologic features as "exuberant proliferation of capillary vessels, often with imperfectly canalized masses of endothelium, massive infiltration with eosinophils and an excess of mast cells, reticulin formation but little collagenous fibrosis and lymphoreticular hyperplasia, increasing with the duration of the lesion and leading to lymphoid follicle formation in lesions of one year or more duration" (8).

ALHE superficially resembles KD because of the similar predilection for the head and neck region, the pathologic findings of a vascular lesion accompanied by lymphoid cells and eosinophils, and treatment by surgical excision. However, recent clinicopathological studies have suggested that these are two separate conditions with different histological and clinical features. While KD has new canalized blood vessels which are lined by flat endothelial cells, ALHE has an exuberant proliferation of new blood vessels which are non-canalized and lined by plump endothelial cells (9,10).

KD is associated with renal disease, particularly nephrotic syndrome (up to 21% of cases), so corticosteroids are also used for treatment (6,11). Recurrence of KD after surgical excision or after stopping corticosteroid use occurs in 25% of cases (7). Non-surgical therapies for KD include corticosteroid treatment, trans-retinoic acid, low dose local radiation therapy and leukotriene receptor antagonists (4). ALHE is not

associated with nephrotic syndrome and the mass may regress spontaneously but in some cases may require surgical excision (9).

Recognizing these diseases as distinctive reactive processes is important, not only to avoid unnecessary treatment such as surgical excision or side effects from the corticosteroid and patient anxiety, but also to advance studies of their etiology and pathogenesis. There have been only a few studies of Kimura disease and ALHE in Thailand, most of which have focused on the clinical management (12-14). To our knowledge, this is the first study to evaluate the clinicopathologic features of KD and ALHE in Thailand. The study also aims to identify criteria for differentiating between KD and ALHE.

Methods

All KD and ALHE cases diagnosed at Maharaj Nakorn Chiang Mai Hospital, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand between January 1, 1999 and December 31, 2011 were analyzed retrospectively with the approval of the institutional review board. Patient demographics and clinical data were retrieved from the electronic medical and pathological records.

All formalin-fixed, paraffin-embedded, 4 µm thick tissue sections from patients which had been stained with hematoxylin-eosin stained (H&E) and mounted on slides were reviewed simultaneously by two pathologists using a multi-headed microscope who were blinded to the previous histologic diagnosis. Discrepant cases were reviewed again and a final consensus diagnosis was reached for the purpose of statistical analysis. The presence of seven histomorphological features were evaluated and recorded for each case including lymphocytic infiltration, presence of lymphoid follicles, tissue eosinophils, stromal fibrosis, presence of plump or flat endothelial cells, presence of canalized or non-canalized blood vessels, and extent of disease. The method for evaluation of lymphocytic infiltration, lymphoid follicles, and tissue eosinophils was eyeball estimation and grading of degree for each morphology: 0 (none), 1+ (mild), 2+ (moderate), 3+ (severe). Lymphocytic infiltration was demonstrated by the infiltration of small lymphocytes into the tissue. The lymphoid follicles had to show hyperplastic process and have prominent germinal centers. Eosinophilic infiltration could be either focal or diffuse. Marked infiltration could reveal an eosinophilic abscess which displayed the area of necrosis. Some plasma cells and histiocytes were

observed, but no multinucleated giant cells were seen. The degrees of each of the morphologies were shown in Figure 1. Stromal fibrosis was defined by the presence or absence of the fibrous band surrounding the lesions as shown in Figure 2. The proliferation of vasculature was categorized as either canalized or non-canalized vessels and the endothelium was rated as either plump or flat in appearance. Canalized vessels were defined by presence of a lumen surrounded by the endothelium while the non-canalized vessels showed no lumen in the center. The flat endothelium was spindle-shaped, while the plump endothelium was swollen. Neither the flat nor plump endothelia showed cytological atypia. Appearances of the blood vessels of each morphology were shown in Figure 3. The extent of disease was demonstrated by the involvement of the tissue as indicated by the degree of incursion of the lesion into deep muscular tissue as shown in Figure 4.

Statistical analysis was carried out using SPSS for Window version 17. The chi-square test and Student's t-test were used to compare means between variables. A *p*-value of less than 0.05 was considered statistically significant.

Results

After reviewing, the 51 cases were categorized into either the KD or the ALHE group. Patient demographics and clinical data are summarized in Table 1. Of the 32 cases in the KD group, 21 were males and 11 females. Age ranged from 2 to 74 years (mean 36.44). All cases presented clinically with painless masses in the head and neck region (*n*=26) including major salivary glands and preauricular masses (*n*=15) plus face, neck, and cervical lymph nodes. Other regions were inguinal (*n*=4), chest wall (*n*=1) and forearm (*n*=1). The size of the masses ranged from 0.4 cm to 10 cm in the greatest dimension (mean 3.75 cm). Regional lymphadenopathy was apparent clinically in 13 patients (40.63%). The patients had symptoms lasting from 1 to 228 months (mean 28.27). At clinical presentation, peripheral blood eosinophilia was documented in 18 of the 32 patients tested (range 2-26.30

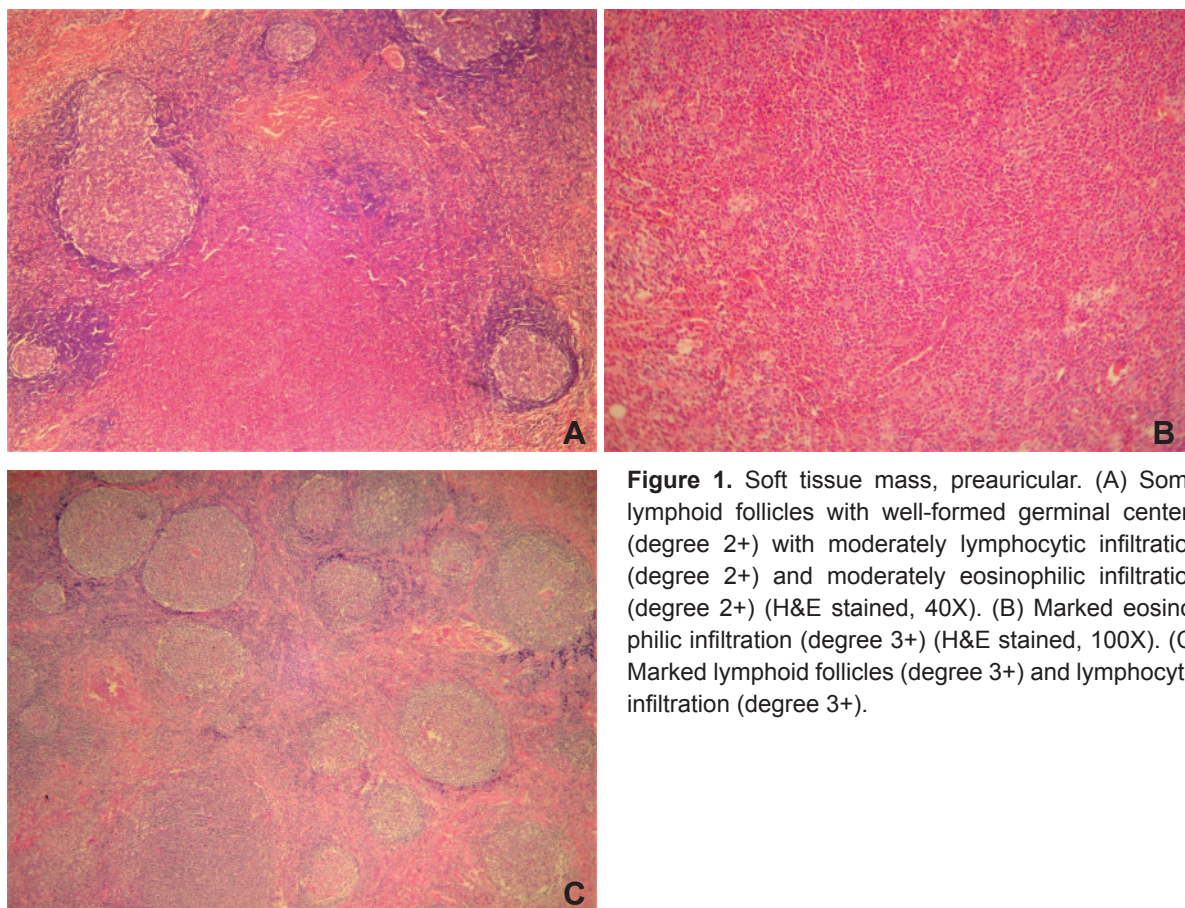


Figure 1. Soft tissue mass, preauricular. (A) Some lymphoid follicles with well-formed germinal centers (degree 2+) with moderately lymphocytic infiltration (degree 2+) and moderately eosinophilic infiltration (degree 2+) (H&E stained, 40X). (B) Marked eosinophilic infiltration (degree 3+) (H&E stained, 100X). (C) Marked lymphoid follicles (degree 3+) and lymphocytic infiltration (degree 3+).

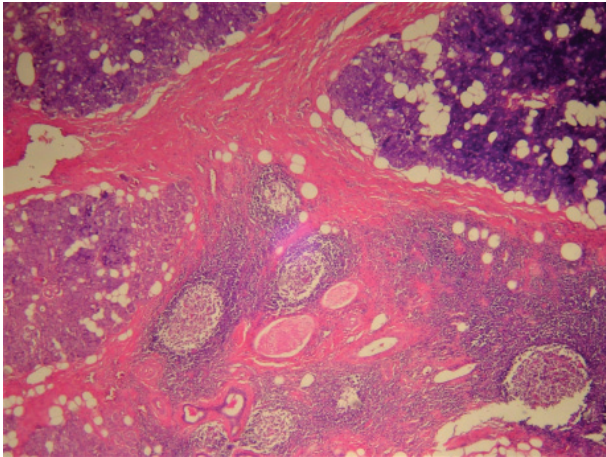
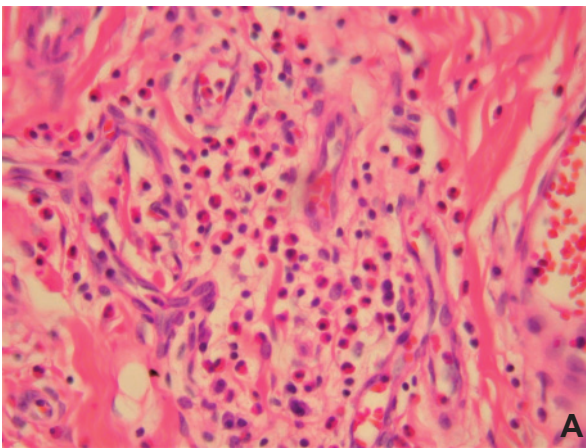
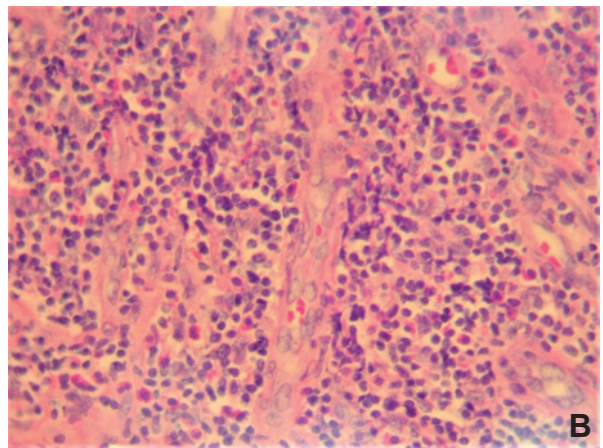


Figure 2. Parotid gland showing the presence of lymphoid follicles (degree 2+) and lymphocytic infiltration (degree 2+) with marked fibrosis. The lesion had invaded the parotid gland. (H&E stained, 20X)



A



B

Figure 3. Vascular proliferation.(A) Flat endothelium. Endothelial cells are spindle-shaped and show the lumen in the center. The vessels were also infiltrated by eosinophils (H&E stained, 400X). (B) plump endothelium. The endothelial cells were swollen. The lumens were narrowing and rare. (H&E stained, 400X).

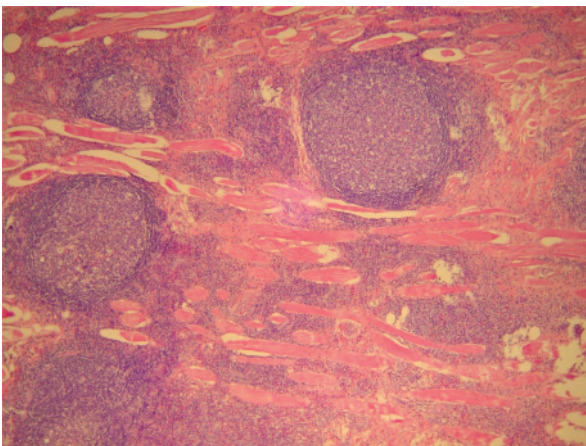


Figure 4. Soft tissue mass. The lesion had invaded the deep muscular layer.

%), while elevated IgE levels were detected in all 4 patients tested (range 37.2-6420 IU/mL). Only one patient had a clinical diagnosis of

nephrotic syndrome (membranoproliferative glomerulonephritis) before developing KD. Of the 19 cases in the ALHE group, 13 were males

Table 1. Patient demographics and comparison of clinical manifestations in KD and ALHE

Patient demographics and clinical manifestations	KD (n=32)	ALHE (n=19)
Age (years) [range, mean]	2-74, 36.44	1-67, 32
Gender [male: female]	21:11	13:6
Symptoms		
1. Chief complaint (n, %)		
- Mass	32, 100	14, 73.70 [†]
- Skin induration	0, 0	2, 10.50
- Cystic lesion	0, 0	1, 5.30
- Nasal obstruction	0, 0	2, 10.50
2. Locations (n, %)		
- Head and neck	26, 81.25	16, 84.21
- Inguinal	4, 12.50	3, 15.79
- Chest wall	1, 3.125	0, 0
- Forearm	1, 3.125	0, 0
3. Lymphadenopathy (n, %)		
- Yes	13, 40.63	4, 21.05
- No	19, 59.37	15, 78.95
4. Duration (months) [range, mean]	1-228, 28.27	1-36, 8.63
5. Size (cm) [range, mean]	0.4-10, 3.75	0.2-3, 1.09
Blood eosinophils (n=30)	2-26.30% (n=18)	3.2-96% (n=12)
Blood IgE (n=4)	37.20-6420 IU/mL	0

[†], $p=0.005$

and 6 females. Their ages ranged from 1 to 66 years (mean 32). The patients presented with firm painless masses (n=14), skin induration (n=2), cystic lesion of the skin (n=1), and nasal obstruction (n=2). The masses measured from 0.2 cm to 3 cm in the greatest dimension (mean 1.09 cm). The involved anatomical regions were the head and neck (conjunctivae, hypopharynx, postauricular, nasal cavity, face, neck and postauricular) in 14 patients and the groin in 3 patients. Superficial lymph nodes were affected in 4 of the 19 patients. Clinical duration of the lesions ranged from 1 month to 36 months (mean 8.63). In 12 patients, peripheral blood eosinophil counts were recorded (3.2-96%). The two patients who had very high blood eosinophil levels also had hypereosinophilic syndrome. Another three patients had associated diseases including fungal infection, HIV infection, and systemic lupus erythematosus. In our study, presentation with a painless mass was statistically significant for a diagnosis of KD ($p = 0.005$).

The histologic review focused on lymphocytic infiltration, lymphoid follicles, tissue eosinophils, stromal fibrosis, endothelium, blood

vessels and the extent of disease. The pathologic features of each disease were summarized in Table 2. Microscopic examination of KD patients revealed a circumscribed aggregation of lymphoid follicles and eosinophils in the subcutaneous tissue including extension into skeletal muscle in some cases. The follicles were hyperplastic with prominent germinal centers. The eosinophilic infiltration can be either focal or diffuse. Either fibrosis surrounded the lesions or fibrous bands extend into the lesion. The fibrous tissue was variably cellular with hyalinization. The vascular lesions showed numerous mature capillaries which were thin-walled and lined with flattened to low cuboidal endothelium. The nuclei were pale and oval. The cytoplasm was scanty and light-staining without vacuolization. Microscopic examination of the ALHE samples revealed vascular proliferation and inflammatory infiltrate. The vascular component showed protruded endothelium with rounded nuclei. One or more cytoplasmic vacuoles could be seen in abnormal endothelial cells. The inflammatory component was characterized by superficial to deep and nodular to diffuse infiltrate, com-

Table 2. Histopathologic features of KD and ALHE

Histopathologic features	KD (n=32)	ALHE (n=19)	<i>p</i> -value
Lymphocytic infiltration			0.054
- Degree 0	0, 0	0, 0	
- Degree 1+	12, 37.50	11, 57.90	
- Degree 2+	16, 50	8, 42.10	
- Degree 3+	4, 12.50	0, 0	
Lymphoid follicles			0.000
- Degree 0	0, 0	11, 57.90	
- Degree 1+	14, 43.80	6, 31.60	
- Degree 2+	12, 37.40	1, 5.30	
- Degree 3+	6, 18.80	1, 5.30	
Tissue eosinophilic infiltration			0.324
- Degree 0	0, 0	0, 0	
- Degree 1+	10, 31.20	7, 36.80	
- Degree 2+	14, 43.80	10, 52.60	
- Degree 3+	8, 25.00	2, 10.60	
Stromal fibrosis			0.257
- Absence	4, 12.50	5, 26.30	
- Presence	28, 87.50	14, 73.70	
Endothelial cells			
- Flat endothelial cells			0.699
Absence	15, 46.90	10, 52.60	
Presence	17, 53.10	9, 47.40	
- Plump endothelial cells			0.136
Absence	17, 53.10	6, 31.60	
Presence	15, 46.90	13, 68.40	
Vessels			
- Canalized vessels			0.590
Absence	11, 34.40	8, 42.10	
Presence	21, 65.60	11, 57.90	
- Non-canalized vessels			0.136
Absence	17, 51.30	6, 31.60	
Presence	15, 46.90	13, 68.40	
Extent of disease ‡			0.029
- Superficial lesion	9, 28.13	8, 42.10	
- Deep lesion	23, 71.87	11, 57.10	

‡ Superficial lesion includes mucosa, skin and superficial lymph node. Deep lesion includes deep subcutaneous tissue, skeletal muscle and parotid gland.

posed predominantly of lymphocytes and a variable number of eosinophils. Lymphoid follicles were rare. The histologic findings differentiating between KD and ALHE were the presence of lymphoid follicles in KD ($p < 0.000$) and the extent of KD into deep subcutaneous tissue, salivary glands, and skeletal muscle ($p = 0.029$).

Discussion

KD usually presented as a painless mass with a predilection for the head and neck region of young Asian men. Even though the disease was more common in males in our study, half the patients in this study were female. A notable number of fourth and fifth decade patients was also noted. These findings added additional characteristics to the known clinical criteria for KD described in previous research

which indicated that the KD occurred almost exclusively in young males (3-7).

The presentation with masses was significantly associated with KD: our study found that the all KD patients had painless masses ($p = 0.005$). On the other hand, ALHE patients presented with a variety of symptoms including masses, nasal obstruction and cysts in the skin. The head and neck region was the most common site in both diseases, 81.25% for KD and 84.2% for ALHE, but other regions were also found, such as inguinal, chest wall and forearm. The average size of a KD mass (3.75 cm) was slightly larger than ALHE (1.09 cm), which agreed with previously published reports, e.g., "KD was usually a large mass (2-5 cm in diameter), but ALHE was usually small (1 cm in diameter) (11).

Previous studies reported that Kimura disease was associated with nephrotic syndrome (up to 21% of cases). Our study showed only one patient with a long history of nephrotic syndrome (membranoproliferative glomerulonephritis or MPGN) prior to developing KD. This might suggest that Kimura disease and MPGN were both related to a Th2 dominant immune response (15,16). On the other hand, ALHE was more frequently associated with hypereosinophilic syndrome and other infections such as fungus and HIV, so those diseases need to be ruled out before reaching a diagnosis of ALHE. Peripheral blood eosinophils and serum IgE might help the clinician to diagnose KD since all cases of KD showed high levels of both in blood tests.

Observed histological features of KD were also concordant with the literature (3-7, 17-19) in the aspects of lymphocytic infiltration, formation of lymphoid follicles with germinal centers, tissue eosinophilia, fibrosis and vascularity. Diagnostic of importance in identifying KD were the presence of lymphoid follicles ($p = 0.000$) and extension of the disease into the deep subcutis, the salivary glands, and skeletal muscle ($p = 0.029$). Together, these findings could help pathologists differentiate KD from ALHE in spite of the fact that both diseases are very similar in terms of clinical and other pathological morphology. Previous studies have identified some

histopathologic differences in the vascular component of the two conditions (17,19). The vascular change of KD shows mainly capillary proliferation and an increased number of thin-walled blood vessels. In contrast, ALHE contains thick-walled blood vessels with the so-called histiocytoid or epithelioid endothelial cells characterized by hypertrophied or vacuolated endothelial cells protruding into the vascular lumen or even occluding the lumen. In our study, however, the vascular component showed no significant difference between the two conditions because both can have canalized as well as non-canalized vessels plus both flat as well as plump endothelial cells in the same lesion. Thus, these characteristics could not be used to the differentiate the two diseases (9,10). A long duration of both diseases does not affect the histological findings because qualitative features such as lymphoid follicles, lymphocytic infiltration and vascular components or fibrosis do not vary over time.

Conclusions

KD is found in females and middle-aged patients, not only young male patients. Findings which would suggest a diagnosis of KD rather than ALHE include presentation with a mass, pathologic findings of lymphoid follicles and extension into deep subcutaneous tissue, skeletal muscle and salivary glands.

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การศึกษาทางคลินิกและจุลพยาธิของโรค Kimura disease และ Angiolymphoid hyperplasia with eosinophilia ในโรงพยาบาลมหาราชนครเชียงใหม่

สฎาณัญญ์ เขาวนศ์ศิลป์ และ พงษ์ศักดิ์ มหานุภาพ
ภาควิชาพยาธิวิทยา คณะแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่

วัตถุประสงค์ ศึกษาลักษณะทางคลินิกและจุลพยาธิของโรค Kimura disease (KD) และ Angiolymphoid hyperplasia with eosinophilia (ALHE)

เครื่องมือและวิธีการศึกษา รวบรวมข้อมูลลักษณะทางคลินิกและพยาธิวิทยาของผู้ป่วยที่ได้รับการวินิจฉัยโรค KD และ ALHE ณ โรงพยาบาลมหาราชนครเชียงใหม่ ระหว่างปี พ.ศ. 2542–2554

ผลการศึกษา ผู้ป่วยโรค KD (ชาย 21 ราย, หญิง 11 ราย) อายุระหว่าง 2-74 ปี (เฉลี่ย 36.44) มีก้อนที่ไม่เจ็บบริเวณศีรษะและลำคอขนาด 0.4-10 เซนติเมตร (เฉลี่ย 3.75) นาน 1-228 เดือน (เฉลี่ย 28.27) ผู้ป่วยโรค ALHE (ชาย 13 ราย, หญิง 6 ราย) อายุระหว่าง 1-66 ปี (เฉลี่ย 32) มีก้อนที่ไม่เจ็บ 14 ราย ขนาด 0.2-3 เซนติเมตร (เฉลี่ย 1.09) อาการอื่นคือ ผิวน้ำเหลือง 2 ราย ถูที่ผิวหนัง 1 ราย และรูขุมขนอุดตัน 2 ราย มีอาการนาน 1-36 เดือน (เฉลี่ย 8.63) จากการศึกษาพบว่า การพบก้อนที่ไม่เจ็บบริเวณศีรษะและลำคอมีความสำคัญทางสถิติกับโรค KD ($p = 0.005$) ความแตกต่างทางลักษณะจุลพยาธิระหว่างโรค KD และ ALHE คือ พบ lymphoid follicles เด่น ($p < 0.000$) รอยโรคอยู่ในชั้นไขมันใต้ผิวหนัง กล้ามเนื้อลาย และก้อนที่ต่อมน้ำลาย ($p = 0.029$) ในโรค KD

สรุปผลการศึกษา KD สามารถพบในผู้ป่วยเพศหญิงและวัยกลางคนได้ ลักษณะทางคลินิกและจุลพยาธิที่ช่วยในการแยกโรคคือ ผู้ป่วยมีก้อน, การพบ lymphoid follicles, รอยโรคอยู่ในชั้นไขมันใต้ผิวหนัง กล้ามเนื้อลาย และก้อนบริเวณต่อมน้ำลาย **เชียงใหม่เวชสาร 2560;56(4):213-21.**

คำสำคัญ: Kimura disease, Angiolymphoid hyperplasia with eosinophilia