THE STUDY OF
HISTOPATHOLOGIC SPECTRUM
IN 59 PATIENTS EXHIBITING CLINICAL FEATURES
OF URTICARIAL VASCULITIS

BY

MISS MATTHASUDA TANTASANEE

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR THE DEGREE OF
MASTER OF SCIENCE (DERMATOLOGY)
CHULABHORN INTERNATIONAL COLLEGE OF MEDICINE
THAMMASAT UNIVERSITY
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was approved as partial fulfillment of the requirements for
the degree of Master of Science (Dermatology)

on May 17, 2017

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Thesis Title	THE STUDY OF HISTOPATHOLOGIC SPECTRUM IN 59 PATIENTS EXHIBITING CLINICAL FEATURES OF URTICARIAL VASCULITIS
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ABSTRACT

Background: Urticarial vasculitis is a variant of cutaneous vasculitis characterized by atypical urticarial lesions that have the classical histopathologic features of leukocytoclastic vasculitis. However, the histologic features of early UV often present with subtle evidences of vasculitis. Therefore, UV is possibly underdiagnosed.

Primary objective: To study the histopathology in patients exhibiting clinical features of urticarial vasculitis

Secondary objective: To study the differences of clinical features and laboratory findings in vasculitis patients and non-vasculitis patients

Methods: The retrospective study reviewed histopathology, clinical records, laboratory findings, and course of diseases in patients diagnosed of urticarial vasculitis at Thammasat University Hospital, Pathum Thani and Phramongkutklao Hospital, Bangkok, Thailand from 2012 to 2017. Patients were divided into 3 groups as the follows: 1) urticarial vasculitis group, 2) compatible with urticarial vasculitis

(CUV) group, and 3) non-vasculitis group by the histologic criteria. The differences of clinical, histopathologic and laboratory findings were studies between each group.

Results: Fifty-nine patients were enrolled in the study. Fourteen patients (23.7%) showed direct evidences of vasculitis and were designated as urticarial vasculitis group. Twenty-three patients (39%) showed secondary changes of vasculitis and were designated as CUV group and 22 patients (37.2%) were diagnosis as non-vasculitis group. There was no statistic significant between the presence of painful lesions, systemic symptoms, response to antihistamine, and high level of ESR in UV and CUV group. Nevertheless, the differences in these factors was presented between the CUV group and non-vasculitis group. The presence of painful lesions, systemic symptoms, response to antihistamine, time to response to treatment, and high ESR level were different between vasculitis group and non-vasculitis group.

Conclusions: Our study showed the diagnosis of UV can be made even minimal secondary changes in histopathologic of vasculitis are present. The presence of painful lesions, systemic symptoms and high ESR level can help the clinician for diagnosis of UV.

Keywords: Urticarial vasculitis, Compatible with urticarial vasculitis, Non-vasculitis, Atypical urticaria, Leukocytoclastic vasculitis

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Miss Matthasuda Tantasanee

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LIST OF ABBREVIATIONS

Symbols/Abbreviations	Terms
UV	Urticarial vasculitis
HUVS	Hypocomplementemic urticarial vasculitis
NUVS	Normocomplementemic urticarial vasculitis
CUV	Compatible with urticarial vasculitis group
NON	Non-vasculitis group
H&E	Hematoxylin & Eosin
IgG	Immunoglobulin G
IgM	Immunoglobulin M
NSAIDs	Nonsteroidal anti-inflammatory drugs
ANA	Antinuclear antibodies
ESR	Erythrocyte sedimentation rate
AST	Aspartate transaminase
ALT	Alanine transaminase
Anti-TG	Antithyroglobulin antibodies
Anti-TPO	Antithyroid peroxidase antibodies
SLE	Systemic lupus erythematosus
RA	Rheumatoid arthritis

CHAPTER 1
INTRODUCTION

1.1 Background and rationale

Urticarial vasculitis is a clinico-pathologic entity characterized by recurrent urticaria that have the histopathologic features of leukocytoclastic vasculitis. Urticarial vasculitis is found approximately 3-20% among chronic urticaria patients (1). The evidence is still not well established in Thailand. The clinical manifestations compatible with urticarial vasculitis including 1) painful, tender, burning or pruritic skin lesions 2) persistence of individual lesions greater than 24 hours, and 3) residual hyperpigmentation or purpura. The systemic symptoms such as fever, joint pain, gastrointestinal symptoms, urinary symptoms, respiratory symptoms etc. might presented in some cases.

UV had the histologic features of leukocytoclastic vasculitis (LCV) which is an essential criteria for diagnosis. The direct evidences of vascular damage include destruction of blood vessels wall with fibrinoid necrosis. The neutrophilic infiltrates surrounding the walls with nuclear dusts. The varied prevalence of UV implies the strictness of the histologic definition for the diagnosis of UV. The collection of the histopathological appearances from large number of urticarial vasculitis patients is necessary for the proper diagnosis.

1.2 Research question

Do the patients in possible UV group have similar symptoms to UV group or non-vasculitis group?

1.3 Specific objective

Primary objective: To study the histopathology in patients exhibiting clinical features of urticarial vasculitis

Secondary objective: To study the difference of clinical features in vasculitis patients and non-vasculitis patients

1.4 Hypothesis

1.4.1 Patients in possible urticarial vasculitis group have clinical features compatible with urticarial vasculitis.

1.4.2 Patients with histopathological features of vasculitis are clinically different from non-vasculitis group.

1.5 Keywords

Urticarial vasculitis
Possible urticarial vasculitis
Non-vasculitis
Atypical urticaria
Leukocytoclastic vasculitis

1.6 Group definition

1.6.1 Urticarial vasculitis group

≥ 2 in 3 of the following histopathologic criteria;

(a) Fibrinoid deposition at blood vessels

(b) Inflammatory cell infiltrate within and around the vessel walls

(c) Destruction of vessel wall

1.6.2 Compatible with urticarial vasculitis group (CUV)

3 of the following histopathologic criteria;

Perivascular inflammatory cells infiltration

Nuclear dust and/or extravasated RBC

No evidence of fibrinoid deposition or vessel wall damage

1.6.3 Non-vasculitis group (NON)

Absence of the histologic criteria in urticarial vasculitis group and compatible with urticarial vasculitis group

1.7 Ethical consideration

The study protocol was approved by;

1) Human Research Ethics Committee of Thammasat University No.1, Faculty of Medicine (Number of COA: 025/2017)

2) Institutional Review Board of Royal Thai Army Medical Department (Number of COA: 486/2560)

1.8 Limitation

There may be some limitations to these findings. As this study was performed as a retrospective review, the data from the medical records, laboratory results and histopathologic examinations, may not be complete.

1.9 Significance of the research

In general, the diagnosis of urticarial vasculitis is made when clinical characteristic is compatible with UV and histopathologic examination shows features of LCV. However, there are some cases that the histopathologic criteria of vasculitis are not clearly established. Therefore, the diagnosis of urticarial vasculitis is depended on the physicians' experiences. Because of the varied histopathological appearance of the urticarial vasculitis, a number of patients still have underdiagnosed.

Therefore, study of the histopathological appearances from large number of urticarial vasculitis patients is necessary for the proper diagnosis.

The benefit of this research is to obtain a better histopathological appearance which can be helpful for the diagnosis UV.

1.10 Time frame

Table 1.1 Time frame

	Jan 2017	Feb 2017	Mar 2017	Apr 2017	May 2017	June 2017	July 2017
Ethic approval							
Data collection							
Data analysis							
Manuscript preparation							
Presentation							
Publication							

CHAPTER 2
REVIEW OF LITERATURE

2.1 Definition

Urticarial vasculitis usually presents with skin lesions compatible with urticaria. Nevertheless, a variety of clinical manifestations were described, ranging from only skin lesions to aggressive, highly morbid, multisystem disorders (1).

Urticarial vasculitis was firstly reported in 1973 by McDuffee and his colleagues. They reported 4 cases of middle aged women who had urticaria and angioedema along with arthritis. They also had gastro-intestinal symptoms such as stomach ache, diarrhea, urinary symptoms including low complement in their blood. Immune complex was found in the blood system resulted in vasculitis (2).

2.2 Epidemiology

The urticarial vasculitis is reported to be about 3-20% of the chronic urticaria (3). UV affects women more than men. It is rare entity that has a peak incidence in the fourth decade of life. It is rare in children and also rare to develop systemic manifestations (1).

2.3 Classification

Urticarial vasculitis can be divided into two groups. 1) normocomplementemic urticarial vasculitis: NUV, and 2) hypocomplementemic urticarial vasculitis: HUV. Both types have similar appearance. However, the HUV's symptoms have severe symptoms compare to NUV (4).

2.4 Clinical manifestation

The clinical appearances of UV are wheals and flares last long for 24-72 hours accompany with purpuric, petechiae, pain symptom and resolved with hyperpigmentation. The lesions can occur on any parts of the body. The study of 72 UV patients from Mehregan and colleagues found thepresence of wheals and flares last long than 24 hours in 64%, purpura in 35%, painful and burning sensation in 32% (4). Beside of urticarial wheals, erythema multiforme-like eruption and bullae can be found but with fewer number (6,7).

The systemic symptoms are also found such as fever, weakness, stomach pain, and joint pain (4). The most common manifestation is musculoskeletal symptoms such as arthralgia or arthritis which can be found between 50-75%. The respiratory and renal symptoms can be found in 20-30%. The most common clinical findings are chronic obstructive pulmonary disease, hemoptysis, proteinuria and hematuria. The gastrointestinal symptoms and ophthalmologic symptoms were reported in 17-30% and 10%, respectively (1).

2.5 Histopathology and immunopathology

The skin biopsy for histopathologic examinations should be done in all suspected patients which can show characteristic features of LCV (1,8). However, the skin biopsy in many cases reveal nonspecific changes. Histologic changes which is widely accepted consisted of the following histopathological criteria:

1) Presence of vascular or endothelial cell damage along with a deposition of fibrinoid material which is called fibrinoid necrosis in postcapillary venule

2) Presence of inflammatory cells surrounding blood vessels or within the vessel walls. The inflammatory cells are composed of neutrophils, eosinophils, lymphocytes and histiocytes. However, the number and type of leukocytes in each case is varied due to the age of lesion when perform the histopathological testing.

Additional features include extravasation of erythrocytes into the surrounding tissue, the presence of leukocytoclasic or swelling endothelial cells might be found. However, these features are not a significant criterion for diagnosis (8).

Direct immunofluorescent (DIF) can demonstrate the immunoglobulins, complements and fibrinogens in the blood vessels and also basement membrane zone which can be found in 79% of the cases in the study from Mehregan DR, et al (4, 9).

IgM, C3 and fibrinogen are the common types which can be seen in 70% of the cases (3,4). The granular depositions at dermo-epidermal junction are seen only in the lesional skin, but not in non-lesional area (2). Seventy percent of the cases who found DIF positive at the dermal-epidermal junction also showed co-existence of renal dysfunction (5).

2.6 Pathophysiology

The mechanism of urticarial vasculitis is caused by type III hypersensitivity reaction (immune complex reaction) (3). A study done by Dienstag and colleagues demonstrated the hepatitis B virus surface antigen-antibody IgM complex deposition within vessels wall and in blood circulation in UV patients with hepatitis B infection (12). In addition, an application of plasmapheresis in order to get rid of the immune complex in blood circulation can relief the condition of urticarial vasculitis (13). These prove an evidence that the cause of urticarial vasculitis is the immune complex. The immune complex formation is caused by the simulation of immune system by unusual proteins from outside, forming up a soluble antigen-antibody complex protein which IgG and IgM are the most common antibody formation (1).

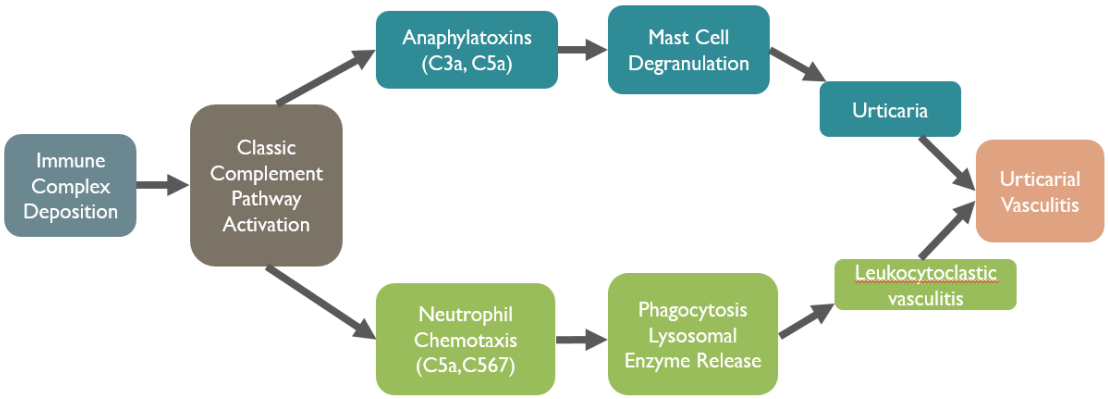

Figure 2.1 Pathophysiology of urticarial vasculitis

This small immune complex can bind to the wall of the blood vessel and stimulates the complement, forming up C5a which is a potent chemotactic factor for neutrophil and increase phagocytic activity. The stimulated neutrophils release proteolytic enzymes (enzymes elastase, collagenase, cathepsin D, cathepsin E and other proteases) which can cause more C5a production and chemotactic more neutrophilic infiltration surrounding blood vessels. The karyorrhexis of neutrophils causes the leukocytoclastic change. Nevertheless, large immune complex will be eliminated by phagocytic cell that are not the cause of vasculitis (43).

Antigen that triggers the reaction is unknown. Surface antigen of hepatitis B and hepatitis C virus, collagen-like region of C1q, other infections and medications have been reported as trigger factors (14).

2.7 Treatments

Urticarial vasculitis is difficult to treat. Depending on the severity of the disease and systemic involvement. Many drugs have been used to treat urticarial vasculitis.

Antihistamine drugs: A drug is used for patients with specific symptoms limitation to skin. This drug is used to control itching. Side effects are low but is not effective in treating inflammation associated with immune complex. It cannot change the progression of the disease (5, 15).

NSAIDS: The most commonly used drugs in this group is indomethacin. This drug is effective up to 50% in treating UV. The common side effects are nausea, vomiting which cannot be tolerated in some patients. This drug can be used in combination with systemic steroid and can help to reduce the dose of steroid usage (5, 13, 15).

Colchicine: It is the common drug used in treatment of cutaneous small-vessel vasculitis. The drugs have side effects such as diarrhea, gastrointestinal side effects, potential teratogenic effect, and cytopenia. Complete blood count should be checked before and after treatment (16).

Dapsone: It is a sulfone drug usually used in recurrent episode of hypocomplementemic urticarial vasculitis (17, 18). The side effects are headache, mild non-hemolytic anemia agranulocytosis and dapsone hypersensitivity syndrome.

Hydroxychloroquine: It is an antimalarial drug. The mechanism of this drug is to inhibit the secretion of lysosomal enzymes, and interleukin-1. Hydroxychloroquine is used in the treatment of urticarial vasculitis limited to skin which is effective around 50 percent (15). The important side effect of hydroxychloroquine is retinopathy. Eye examination should be done before and after treatment two times a year.

Corticosteroid: This drug causes good result. The treatment dose depends on the severity of the disease (10). The recurrent episodes can occur after stop taking the drug. The effectiveness can be increased by using corticosteroid combined with the azathioprine, low-dose gold therapy, cyclophosphamide and cyclosporine (4, 5, 17, 20).

Azathioprine: This drug acts through the mechanisms affecting DNA transcription. The major side effect is the leukopenia. Caution should be take when using azathioprine in combination with the xanthine-oxidase inhibitor which 5 times dose of azathioprine from normal dose should be reduced. Azathioprine combines with systemic steroid is effective to treat urticarial vasculitis with renal involvement (21, 22).

Other drugs such as cyclophosphamide, cyclosporine A, interferon-alpha have been reported in treating urticarial vasculitis (23, 24, 25).

CHAPTER 3
RESEARCH METHODOLOGY

3.1 Research design

This research is retrospective review. The medical records and histopathologic slide for review will be conducted at Department of Dermatology, Thammasat University Hospital and Phramongkutklao Hospital between January 1, 2012 and February 28, 2017.

3.2 Target populations

3.2.1 Inclusion criteria

Thai patients at all aged, both male and female who had urticarial wheals accompanied with the following criteria

1) Lesions lasted longer than 24 hours
2) Leaving hyperpigmentation or purpura

3.2.2 Exclusion criteria

1) Incomplete medical records and/or unable to obtain slides or paraffin blocks.

2) Patients with a history of taking anti-inflammatory drugs including steroids and nonsteroidal anti-inflammatory drugs, colchicine, hydroxychloroquine or dapsone before doing a skin biopsy at least 4 weeks.

3.2.3 Sample size

Table 3.1 Sample size calculation

$$n = \frac{Z^2 P (1-P)}{d^2}$$

$$= \frac{1.96^2 \times 0.42 \times 0.58}{(0.3 \times 0.42)^2}$$

$$= 59$$

Where:

n = sample size

Z = Z statistic for a level of confidence (95% level of confidence used, Z value is 1.96)

P = expected prevalence of proportion of vasculitis in patients with clinical features of UV

d = precision (30% of P)

3.3 Research methodology

3.3.1 Data collection

The data collected in this study clinical symptoms (morphology of the lesions, duration, additional systemic symptoms), treatments and the response after treatment.

3.3.2 Histopathological examination

Histopathological features of the skin biopsy will be re-examination by the 3 investigators (principle researcher and 2 dermatopathologists). The consensus will be made on the 2 out of 3 opinions.

3.3.3 Research grouping

Patients will be divided into 3 groups by the following criteria of histologic findings:

3.3.3.1 Urticarial vasculitis group

≥ 2 in 3 of the following histopathologic criteria;

(a) Fibrinoid deposition at blood vessels

(b) Inflammatory cell infiltrate within and around the vessel walls

(c) Destruction of vessel wall

3.3.3.2 Compatible with urticarial vasculitis group

3 of the following histopathologic criteria;

(a) Perivascular inflammatory cells infiltration

(b) Nuclear dust and/or extravasated RBC

(c) No evidence of fibrinoid deposition or vessel wall damage

3.3.3.3 Non-vasculitis group

Absence of the histologic criteria in urticarial vasculitis group and compatible with urticarial vasculitis group

3.4 Outcome measurement

3.4.1 Clinical characteristics

The number of the patients, clinical manifestations of skin lesions, systemic symptoms, laboratory results will be recorded.

3.4.2 Histopathology

Histopathological results will be recorded and evaluate the intensity of inflammatory cells as followed:

Table 3.2 Histopathological records

Vascular injury - Superficial infiltrate - Deep infiltrate - Perivascular inflammatory cell infiltrate - Interstitial infiltrate - Intensity of cells - Fibrinoid deposition in vessel wall - Destruction of the vessel wall - Fibrin thrombi in vessel lumen - Leukocytoclasis - Extravasation of RBC - Dermal edema - Pure cell infiltrate - Mixed cell infiltrate - Cell infiltrate (grade 0-4) - Neutrophil - Lymphocyte - Eosinophil	
Other findings:	

3.5 Definition

Our study uses the following definitions;

1) **Response to antihistamine** is defined as decreasing of wheal more than 50% within 2 weeks after receiving antihistamine.

2) **Relapse** is defined as flare up of wheal after all the symptoms are resolved for 1 month.

3) **Response to overall treatment** is defined as decreasing of wheal more than 50% within 1 month after receiving overall treatment.

4) **Improvement** is defined as all the patients' symptoms are resolved without relspse.

5) **Intensity of inflammatory cells infiltrate** was grading by perivascularly and interstitially in the dermis area as follows:

Grade 1 = <25%

Grade 2 = 26-50%

Grade 3 = 51-75%

Grade 4 = >75%

6) **Grading of inflammatory cell type infiltrate** (neutrophil, lymphocyte, and eosinophil) was grading by:

Grade 0 = 0%

Grade 1 = 1-25%

Grade 2 = 26-50%

Grade 3 = 51-75%

Grade 4 = 76-100%

3.6 Data collection

1) Age, gender, occupation (without name, surname, H.N.) with a code created for each patient.

2) Data about the illness consisted of characteristics of the urticaria, duration of urticaria, pigmentation after the urticarial disappear, pain and itches, coexistence of other systemic symptoms consisted of fever, arthralgia, muscle pain, ophthalmologic problems, pulmonary disease, gastrointestinal and renal symptoms.

3) Past history of any disease consisted of underlying diseases, allergic to drug or food, recurrent of urticaria and former treatment received.

4) Physical examination will be taken, characteristics of the wheals, location, and the spreading of the wheal.

5) Laboratory findings

6) Results from histopathological examination.

7) Treatment given and the response to treatment

All data will be recorded in a record form as followed:

CASE RECORD FORM

Code no. _____ Slide no._____

Age at diagnosis _____ Gender _____ Date of birth ___/___/____

Date of diagnosis ___/___/_____

Date of skin biopsy ___/___/_____

Chief complaint _____

Duration of illness_____ Underlying

disease_____

CLINICAL RECORD

Urticarial wheal : Duration _____ hr.

Location _____

Clinical findings	Yes	No	N/A
Persist more than 24 hr.			
Residual hyperpigmentation or purpura			
Painful or burning sensation than itch			

Other clinical findings:

_____

_____

Trigger factors: _____

Drug taking: _____

Duration: _____ Response to drug: _____

Systemic symptoms:

_____

_____

LABORATORY DATA

_____

_____

TREATMENT

Drug:

_____

_____

Date of improvement _____ Last follow up date_____

HISTOLOGIC DATA

Vascular injury
- Superficial infiltrate
- Deep infiltrate
- Perivascular inflammatory cell infiltrate
- Interstitial infiltrate
- Intensity of cells
- Fibrinoid deposition in vessel wall
- Destruction of the vessel wall
- Fibrin thrombi in vessel lumen
- Leukocytoclasis
- Extravasation of RBC
- Dermal edema
- Pure cell infiltrate
- Mixed cell infiltrate
- Cell infiltrate (grade 0-4)
  - Neutrophil
  - Lymphocyte
  - Eosinophil	

Other findings:	

Figure 3.1 Case record form

3.7 Data analysis

This research is a cross sectional descriptive study. Data will be analysed as followed:

8.1 Quantitative analysis of data including number, percentage, will be analysed by mean and standard deviation.

8.2 Qualitative analysis of data including characteristics of wheals, degree of pathology, histopathologic findings will be analysed by frequency.

8.3 Classify of pathological characteristics into 3 groups; the urticarial vasculitis, the dense infiltrate and urticarial group. Comparison of data found between 3 groups. Test of differences between groups by Chi-square at the .05 level of significance.

3.8 Conceptual framework

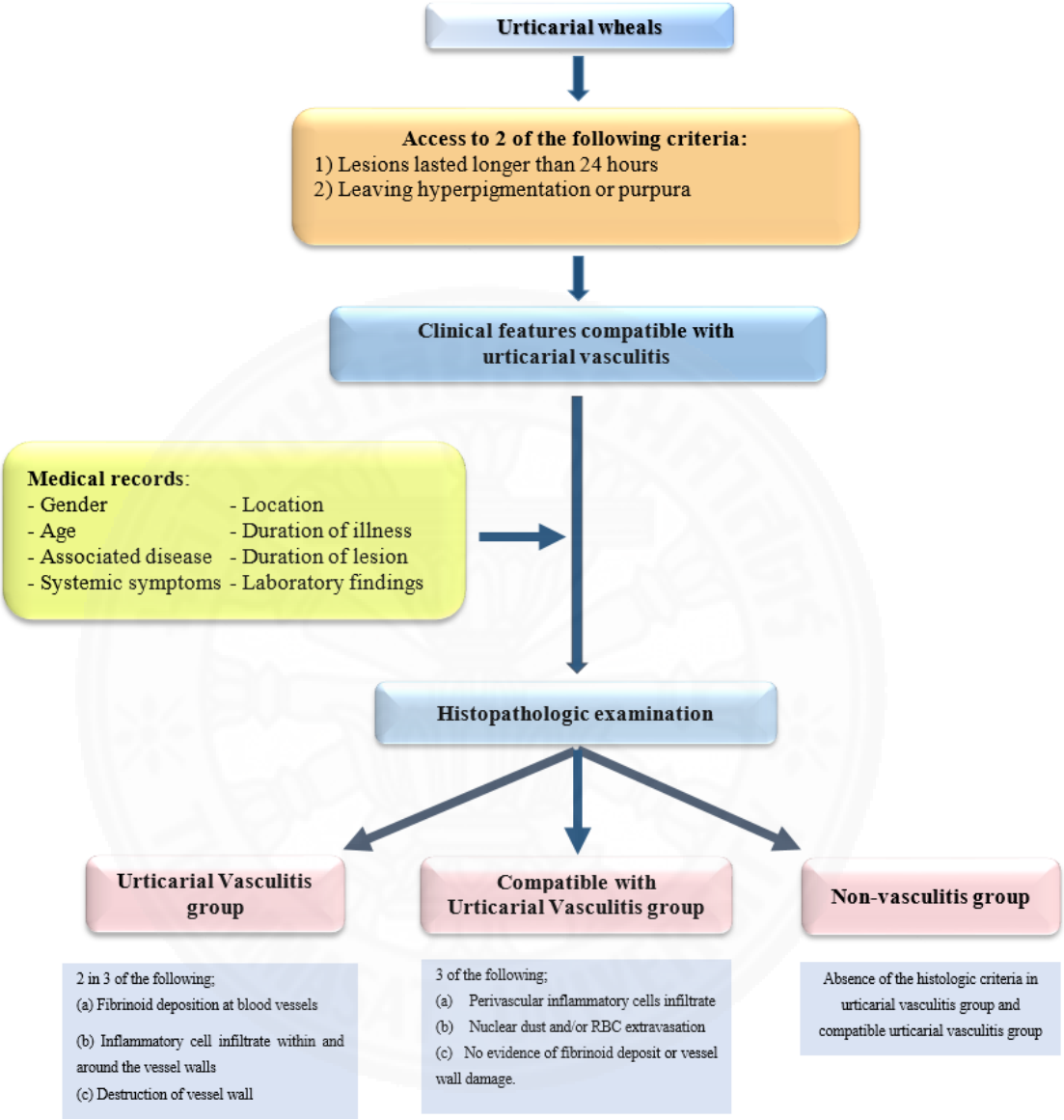

Figure 3.2 Conceptual framework

CHAPTER 4
RESULTS

This chapter represents data analysis in regard of 59 patients. Statistical analysis was performed with the IBM SPSS for Windows. Both descriptive and inferential analysis was selected to interpret collected data. In term of descriptive analysis, frequency, percentage, range, mean and standard deviation was applied to summarise patient data, clinical data, response to treatment, and laboratory data. Crosstab analysis with Chi-square test of association was selected to compare dichotomous data, and independent t-test was applied to identify continuous data between (1) vasculitis group and non-vasculitis group (2) UV and compatible with urticarial vasculitis group (CUV), and (3) CUV and non-vasculitis group.

The patients were those who received medical treatments in Thammasat University Hospital & Phramongkutklao Hospital. Every patient was diagnosed with such clinical manifestations as 1) persistent wheal greater than 24 hours and 2) residual purpura or hyperpigmentation. Each patient has undergone physical examinations, laboratory investigations, and histopathologic examinations. Fifty-nine patients were enrolled in this study which 13 patients were men and 46 patients were women (ratio of 1:3.5). The mean age was 45.5 years (ranging from 7 to 81 years).

All the histopathologic slides were re-elavulated. Thirty-seven patients had leukocytoclastic vasculitis which divided by histopathologic features into “urticarial vasculitis group” (n=14, 23.7%) and “compatible with urticarial vasculitis group” (n=23, 39%).

Twenty-two patients had no feature of vasculitis and were classified under “non-vasculitis group” (n=22, 37.2%).

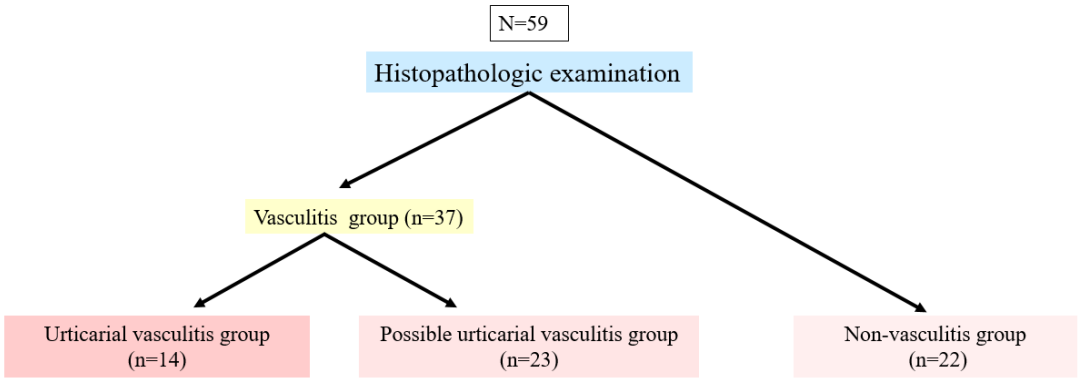

Figure 4.1 Patients grouping by histopathologic features

4.1 Differences between vasculitis group and non-vasculitis groupPatient Population

From table 1, vasculitis group was diagnosed in 37 of 59 (62.7%) and urticarial group consists of 22 of 59 patients (37.3%). Differences between patients with vasculitis group and patients with non-vasculitis group are shown in table 4.1. The majority in vasculitis group is female (73%). with 13 men and 46 women (ratio of 1:3.5) (figure 4.2). Ages in vasculitis group are between 23 and 81 years old, and average age is 45 years. Furthermore, majority of non-vasculitis group is also female (86.4%). Ages in non-vasculitis group are between 7 and 74 years old, and average age is 47 years. There was no statistic significant in the demographic data between vasculitis and non-vasculitis groups.

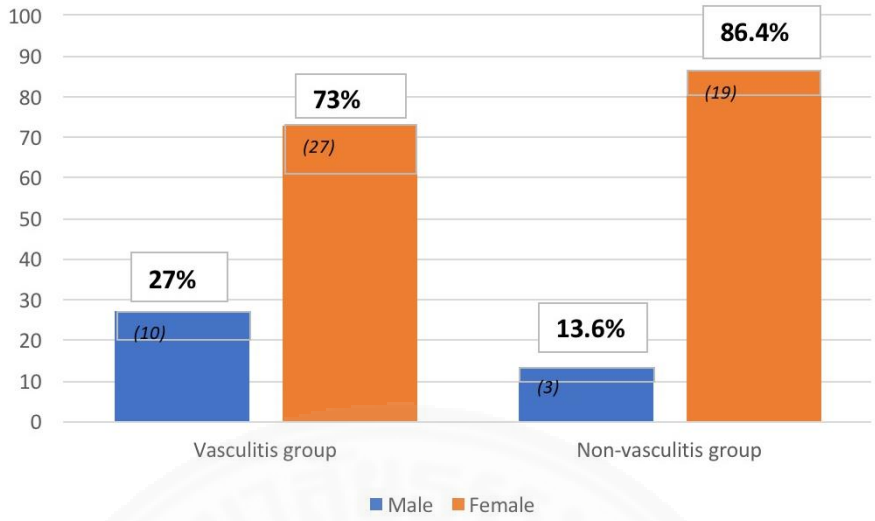

Figure 4.2 Male-Female in vasculitis and non-vasculitis group

Main Clinical Features

According to clinical data, four patients of vasculitis group (10.8%) had underlying autoimmune diseases including autoimmune thyroiditis (n=2, 5.4%), systemic lupus erythematosus (n=1, 2.7%), and rheumatoid arthritis (n=1, 2.7%). Two patients of non-vasculitis (9.1%) group had underlying autoimmune diseases including autoimmune thyroiditis (n=1, 4.5%) and rheumatoid arthritis (n=1, 4.5%). There was no statistic significant in the underlying autoimmune diseases between these 2 groups.

The trigger factors were identified in 24.3% in vasculitis group and 18.2% in non-vasculitis group which was shown no statistic significant (table 4.1).

The mean duration of illness was 34.24±73 days in vasculitis group and 74.18±126.86 days in non-vasculitis group. The duration of wheal was 6.35±5.49 days in vasculitis group and 6.35±5.49 days in non-vasculitis group. These findings showed no statistic significant between the 2 groups.

Majority of vasculitis group had painful symptom (37.8%) when compare to non-vasculitis group (4.5%) which showed statistic different between these 2 groups ($p < 0.05$). The skin lesions presented with plaques and papules and usually located on arms, trunk and face/neck which were similar in both groups.

The systemic symptoms were presented 32.4% in vasculitis group and 9.1% in non-vasculitis group as shown in figure 4.3.

It shows no difference between trigger factors of vasculitis group (24.3%) and non-vasculitis group (18.2%) at 0.05 significant level.

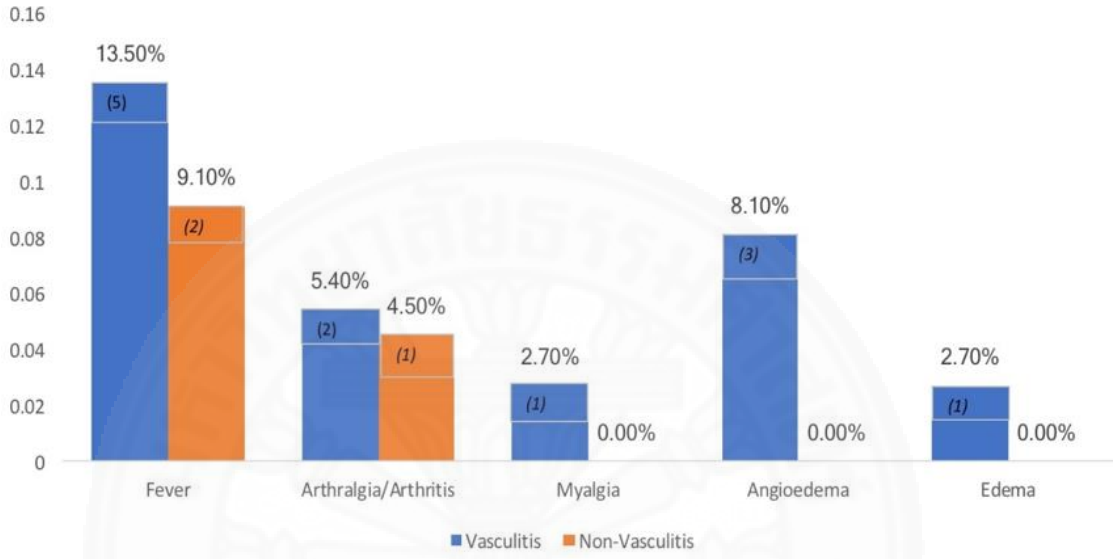

Figure 4.3 Systemic symptoms in vasculitis and non-vasculitis group

Almost all patients in both groups (97.3% in vasculitis group and 100% in non-vasculitis group) received anti-histamines. Non-vasculitis group had more response to antihistamine treatment compared to vasculitis group in significant level (81.8% vs 47.2%, $p < 0.05$). The patients in vasculitis group received prednisolone more number than the patients in non-vasculitis group which showed statistic significant (73% vs 36.4%, $p < 0.05$). Other medications such as colchicine, indomethacin showed no statistic significant between the 2 groups.

According to the response to overall treatment, and relapse, no statistic significant was detected between the 2 groups.

Vasculitis group had significant longer time to response to overall treatment compare to non-vasculitis group (34±44.73 days vs 16.14±14.68 days, $p<0.05$).

The laboratory tests were not done in all patients. The laboratory data included CBC, ANA, viral hepatitis profile, creatinine, ESR, TFT, Anti-TG Ab,

Anti-TPO Ab, Liver function test, urine analysis, C3, and C4. The results were as the follows:

CBC was done in 23 patients of vasculitis group (62.1%) and 16 patients in non-vasculitis group (72.7%). The abnormal results were observed in 5 patients as shown in table 4.1.

ANA was done in 16 patients of vasculitis group (43.2%) and 10 patients in non-vasculitis group (45.5%). Six patients of vasculitis group and non-vasculitis group were positive ANA.

Viral Hepatitis Profile was done in 15 patients of vasculitis group (40.5%) and 9 patients of non-vasculitis group. It shows all patients who tested hepatitis profile is normal ($p > 0.05$).

Creatinine was done in 21 patients of vasculitis group (56.8%) and 13 patients of non-vasculitis group (59%)**.** It shows all patients who tested creatinine is normal ($p > 0.05$).

ESR was done in 11 patients of vasculitis group (29.7%) and 3 patients in non-vasculitis group (13.6%). ESR was considered high when it was higher than 15 mm/h for male or 20 mm/h for female patients. Nine patients in vasculitis group (81.8%) had high ESR titer, while none of patient in non-vasculitis group had high ESR titer. It showed statistic significant between the 2 groups ($p<0.05$). Nevertheless, there was no statistic significant was detected in mean of ESR level.

However, underlying pathologies can also be a possible cause of elevated ESR including collagen vascular disease, infectious disease, fever, malignancy, or hematological problem.

Excluding other possible causes that increasing the ESR level, 5 patients in vasculitis group (71.4%) had high ESR and two patients in non-vasculitis (100%) had normal ESR. There were no differences of high ESR titer and mean of ESR level between vasculitis and non-vasculitis group ($p>0.05$).

Thyroid function test was done in 8 patients of vasculitis group (21.6%) and 7 patients in non-vasculitis group (31.8%). Vasculitis group has 1 patient of hyperthyroidism (12.5%) and 1 patient of hypothyroidism (12.5%). All seven patients in non-vasculitis group have normal thyroid function test. There was one

patient of positive anti-TG (100%) and one patient of positive for anti-TPO (100%) in vasculitis group, while non-vasculitis group has 2 patients of positive anti-TG (100%). There was no statistical significance.

Liver function test was done in 17 patients of vasculitis group (45.9%) and 10 patients in non-vasculitis group (45.5%). High level was detected in 3 patients of vasculitis group and 2 patients of non-vasculitis group.

Stool examination and urine analysis were done in 10 patients and 25 patients, respectively in vasculitis group and all were normal.

C3 and C4 complement were done in 4 patients in vasculitis group (10.8%) only and all were normal C3 level. Only one patient had low level C4.

Table 4.1 The features of patients in vasculitis group (VAS) and patients in non-vasculitis group (NON)

	VAS vs NON				p-value
	VAS (n = 37)		NON (n = 22)		
Demographic data					
Gender					
Male	10	27.0%	3	13.6%	.230
Female	27	73.0%	19	86.4%	
Age (Mean ± S.D) [range] (years)	44.86±17.56 [23-81]		46.68±17.34 [7-74]		.701
Clinical data					
Trigger factors	9	24.3%	4	18.2%	.582
Drug	3	33.3%	1	4.5%	.403
Herb	0	0.0%	2	9.1%	.062
Seafood	2	5.4%	1	4.5%	.884
Tetanus toxin	1	2.7%	0	0.0%	.437
Exercise	1	2.7%	0	0.0%	.437
Glutathione	1	2.7%	0	0.0%	.437
Infection	1	2.7%	0	0.0%	.437

Table 4.1 The features of patients in vasculitis group (VAS) and patients in non-vasculitis group (NON) (Cont)

	VAS vs NON				p-value
	VAS (n = 37)		NON (n = 22)		
Underlying autoimmune	4	10.8%	2	9.1%	.833
Autoimmune thyroiditis	2	5.4%	1	4.5%	.884
System lupus erythematosus	1	2.7%	0	0.0%	.437
Rheumatoid arthritis	1	2.7%	1	4.5%	.705
Duration of illness (Mean ± S.D) (days)	34.24±73.00		74.18±126.86		.187
Skin lesion					
Duration of wheal (Mean ± S.D) (days)	6.35±5.49		7.00±12.20		.780
Painful	14	37.8%	1	4.5%	.005
Plaques	36	97.3%	22	100.0%	.437
Papules	6	16.2%	3	13.6%	.790
Location					
Trunk	30	81.1%	14	63.6%	.137
Arms	31	83.8%	16	72.7%	.308
Legs	32	86.5%	18	81.8%	.630
Face/Neck	9	24.3%	4	18.2%	.582
Systemic symptoms	12	32.4%	2	9.1%	.042
Arthritis & arthralgia	2	5.4%	1	4.5%	
Edema	1	2.7%	0	0.0%	
Fever	5	13.5%	2	9.1%	
Angioedema	3	8.1%	0	0.0%	
Myalgia	1	2.7%	0	0.0%	
Response to treatment					
Anti-histamine taking	36	97.3%	22	100.0%	.437
Response to anti-histamine	17	47.2%	18	81.8%	.009

Table 4.1 The features of patients in vasculitis group (VAS) and patients in non-vasculitis group (NON) (Cont)

	VAS vs NON				p-value
	VAS (n = 37)		NON (n = 22)		
Colchicine taking	10	27.0%	8	36.4%	.451
Prednisolone taking	27	73.0%	8	36.4%	.006
Indomethacin taking	3	8.1%	4	18.2%	.247
Others					
Cyclosporine	2	5.4%	0	0.0%	.267
Methotrexate	1	2.7%	0	0.0%	.437
Azathioprine	1	2.7%	0	0.0%	.437
Response to overall treatment	30	81.1%	19	86.4%	.601
Time to response (Mean ± S.D) (days)	34±44.73		16.14±14.68		.030
Time to improvement (Mean ± S.D) (days)	43.33±58.4		32.8±53.95		.364
Relapse	4	10.8%	1	4.5%	.403
Laboratory findings					
Complete blood count :	23	62.1%	16	72.7%	
Normal	19	82.6%	16	100.0%	.078
Anemia	2	8.7%	0	0.0%	.226
Leukocytosis	1	4.3%	0	0.0%	.398
Thrombocytopenia	1	4.3%	0	0.0%	.398
ANAs	16	43.2%	10	45.5%	
Negative	10	62.5%	4	40%	
Positive	6	37.5%	6	60.0%	.263
Speckled	3	50.0%	5	83.3%	.221
Cytoplasm	1	16.7%	0	0.0%	.296
Homogenous	2	33.3%	0	0.0%	.121
Nucleolar	0	0.0%	2	33.3%	.121

Table 4.1 The features of patients in vasculitis group (VAS) and patients in non-vasculitis group (NON) (Cont)

	VAS vs NON				p-value
	VAS (n = 37)		NON (n = 22)		
Viral hepatitis profile	15	40.5%	9	40.9%	
Normal	15	100.0%	9	100.0%	-
Creatinine	21	56.8%	13	59%	
Normal	21	100.0%	13	100.0%	-
ESR	11	29.7%	3	13.6%	
(Mean ± S.D)	43.64±33.88		15.50±4.93		.172
Normal	2	16.7%	3	100.0%	.009
High (>15mm/h in men, or >20mm/h in women)	9	81.8%	0	0.0%	.009
ESR (without possible cause)	7	18.9%	2	9.0%	
(Mean ± S.D)	33.43±22.25		16.00±5.66		.329
Normal	2	28.6%	2	100.0%	.073
High (>15mm/h in men, or >20mm/h in women)	5	71.4%	0	0.0%	.073
Thyroid function test	8	21.6%	7	31.8%	
Normal	6	75.0%	7	100.0%	.155
Hypothyroidism	1	12.5%	0	0.0%	.333
Hyperthyroidism	1	12.5%	0	0.0%	.333
Anti-TG	1	2%	2	9%	
positive	1	100.0%	2	100.0%	-
Anti-TPO	1	2%	2	9%	

Table 4.1 The features of patients in vasculitis group (VAS) and patients in non-vasculitis group (NON) (Cont)

	VAS vs NON				p-value
	VAS (n = 37)		NON (n = 22)		
Normal	0	0.0%	2	100.0%	-
Positive	1	100.0%	0	0.0%	-
Liver function test	17	45.9%	10	45.5%	
Normal	14	82.3%	8	80.0%	-
Transaminitis	3	17.7%	2	20.0%	-
Stool examination	7	18.9%	3	13.6%	
Normal	7	100.0%	3	100.0%	-
Urine analysis	15	40.5%	10	45.5%	
Normal	15	100.0%	10	100.0%	-
C3	4	10.8%	0	0.0%	
Normal	4	100.0%	0	0.0%	-
C4	4	10.8%	0	0.0%	
Normal	4	80.0%	0	0.0%	-
low	1	20.0%	0	0.0%	-

From histopathologic examination between patients with vasculitis group and patients with non-vasculitis group, all of patients showed superficial infiltration. Sixty-two-point-two percent of vasculitis group and 45.5% of non-vasculitis group took deep infiltration. A hundred percent of vasculitis group and 95.5% of non-vasculitis group showed perivascular infiltration.

However, majority of vasculitis group (86.5%) was taken interstitial infiltration, while only 45.5% of non-vasculitis group took this pattern ($p <$

0.05). According to intensity of cell, majority of non-vasculitis group presented grade 1 (77.3%) and grade 2 infiltration (22.7%) without grade 3 and 4 infiltration. The vasculitis group presented all patterns included grade 1, grade 2 and grade 3 infiltration in 40.5%, 45.9% and 13.5%, respectively. Dermal edema was not difference in both groups which was found in 8 patients (21.6%) of vasculitis group and 2 patients (9.1%) of non-vasculitis group. From vasculitis group, it found 18.9% presented fibrinoid deposit at vessel wall, 32.4% presented vessel wall damaged, 62.2% had nuclear dust, 67.6% had extravasated RBC and 8.1% presented fibrin thrombi in blood vessel. Nevertheless, none of the patients in non-vasculitis group presented all of these features.

Depending on the types of inflammatory cells infiltrations, vasculitis group had all types of cells. Even non-vasculitis group also presented all types of cells, majority of the patients had no neutophils which showed statistic significant compare to vasculitis group (table 2).

Table 4.2 The histopathologic examinations in vasculitis group (VAS) and non-vasculitis group (NON)

	VAS vs NON				p-value
	VAS (n = 37)		NON (n = 22)		
Superficial infiltrate	37	100.0%	22	100.0%	-
Deep infiltrate	23	62.2%	10	45.5%	.211
Perivascular infiltrate	37	100.0%	21	95.5%	.880
Interstitial infiltrate	32	86.5%	10	45.5%	.001
Intensity of cell infiltrate					
Grade 1 (<25%)	15	40.5%	17	77.3%	.006
Grade 2 (26-50%)	17	45.9%	5	22.7%	.075
Grade 3 (51-75%)	5	13.5%	0	0.0%	.071
Grade 4 (>75%)	0	0.0%	0	0.0%	-
Dermal edema	8	21.6%	2	9.1%	.215
Fibrinoid deposit at vessel wall	7	18.9%	0	0.0%	-
Vessel wall damaged	12	32.4%	0	0.0%	-

Table 4.2 The histopathologic examinations in vasculitis group (VAS) and non-vasculitis group (NON) (Cont)

	VAS vs NON				p-value
	VAS (n = 37)		NON (n = 22)		
Nuclear dust	23	62.2%	0	0.0%	-
Extravasated RBC	25	67.6%	0	0.0%	-
Fibrin thrombi in blood vessel	3	8.1%	0	0.0%	.170
Neutrophilic infiltrate					
0%	5	13.5%	13	59.1%	.000
1-25%	13	35.1%	7	31.8%	.795
26-50%	12	32.4%	2	9.1%	.042
51-75%	5	13.5%	0	0.0%	.071
76-100%	2	5.4%	0	0.0%	.267
Lymphocytic infiltrate					
0%	-		-		
1-25%	5	13.5%	0	0.0%	.071
26-50%	9	24.3%	2	9.1%	.146
51-75%	12	32.4%	2	9.1%	.042
76-100%	11	29.7%	18	81.8%	.000
Eosinophilic infiltrate					
0%	7	18.9%	3	13.6%	.601
1-25%	25	67.6%	17	77.3%	.426
26-50%	3	8.1%	1	4.5%	.599
51-75%	2	5.4%	1	4.5%	.884
76-100%	-		-		

4.2 Differences between urticarial vasculitis group(UV) and compatible with urticarial vasculitis group(CUV)

From table 4.3, UV was diagnosed in 14 of 59 (23.7%) and CUV consists of 23 of 59 patients (39%). Majority of the patients in UV and CUV were female which mean age 46 and 44 years as shown in table 3. No difference in demographic data, clinical manifestations, possible trigger factors and underlying autoimmune diseases between this 2 groups was demonstrated.

The duration of illness, duration of wheal and skin lesion showed no difference between the 2 groups. More number of the patients in CUV had lesions located on trunk which was showed statistic significant compare to the UV group.

The systemic symptoms can be found in both group without statistic significant.

The patients in both groups received the similar treatment with anti-histamines, colchicine, indomethacin and prednisolone without statistic difference. Additionally, no difference in the course of disease was detected in both group which included the response to anti-histamines, length of time to improvement, time to response and relapse.

The laboratory findings between this 2 groups showed no difference as shown in table 3. The results were as the follows:

CBC was done in 10 patients of UV (71.4%) and 13 patients in CUV (72.7%). The abnormal results were observed in 5 patients in CUV as shown in table 4.3.

ANA was done in 5 patients of UV group (35.7%) and 11 patients in CUV (47.8%). Two patients of UV group (40%) and 4 patients in CUV (36.4%) group were positive ANA with no statistic significant.

Viral Hepatitis Profile was done in 4 patients of UV (28.5%) and11 patients of CUV. It shows all patients who tested hepatitis profile is normal ($p > 0.05$).

Creatinine was done in 7 patients of UV (50%) and 11 patients of CUV (60.9%)**,** It shows all patients who tested creatinine is normal ($p > 0.05$).

ESR was done in 4 patients of UV (28.5%) and 7 patients in CUV (30.4%). Three patients in UV group (60%) had high ESR titer, while six patients in

CUV had high ESR titer (85.7%). It showed no statistic significant between the 2 groups ($p>0.05$). There was no statistic significant was detected in mean of ESR level.

Thyroid function test was done in 3 patients of UV group (21.4%) and 5 patients in CUV (21.7%). All patients in UV group had normal test. In CUV group, 1 patient had hyperthyroidism (20%) and 1 patient had hypothyroidism (20%). There was no statistical significance of thyroid function test between 2 groups. Anti-TG and Anti-TPO were tested in one patient of CUV who had hyperthyroidsim with positive results (100%).

Liver function test was done in 6 patients of UV group (42.9%) and 11 patients in CUV (47.8%). Three patients in CUV (27.7%) had transaminitis.

Stool examination was done only in 7 patients of CUV (30.4%) and all were normal.

urine analysis was done in 5 patients of UV (35.7%) and 10 patients of CUV (43.4%) and all were normal.

C3 and C4 complement, C3 was done in 1 patient of UV (7.1%) and 3 patients of CUV (13%), and all were normal C3 level. C4 was done in 2 patients of UV (14.2%) and 3 patients of CUV (13%). Only one patient in UV had low level C4 (50%).

Table 4.3 The features of patients in urticarial vasculitis group (UV) and patients in compatible with urticarial vasculitis group (POS)

	UV vs CUV				p-value
	UV (n = 14)		CUV (n = 23)		
Demographic data					
Gender					
Male	4	28.6%	6	26.1%	.869
Female	10	71.4%	17	73.9%	
Age (Mean ± S.D) [range] (years)	45.64±16.21 [24-80]		44.39±18.67 [23-81]		.837
Clinical data					
Trigger factors	2	14.3%	7	30.4%	.267
Drug	1	7.1%	2	8.7%	.867
Herb	-		-		-
Seafood	0	0.0%	2	8.7%	.257
Tetanus toxin	0	0.0%	1	4.3%	.429
Exercise	1	7.1%	0	0.0%	.194
Glutathione	0	0.0%	1	4.3%	.429
Infection	0	0.0%	1	4.3%	.429
Underlying autoimmune	2	14.3%	2	8.7%	.595
Autoimmune thyroiditis	1	7.1%	1	4.3%	.715
System lupus erythematosus	0	0.0%	1	4.3%	.429
Rheumatoid arthritis	1	7.1%	0	0.0%	.194
Duration of illness (Mean ± S.D) (days)	43.93±70.92		28.35±75.18		.537
Skin lesion					
Duration of wheal (Mean ± S.D) (days)	6.50±6.01		6.26±5.29		.900
Painful	6	42.9%	8	34.8%	.623
Plaques	13	92.9%	23	100.0%	.194
Papules	2	14.3%	4	17.4%	.804

Table 4.3 The features of patients in urticarial vasculitis group (UV) and patients in compatible with urticarial vasculitis group (POS) (Cont)

	UV vs CUV				p-value
	UV (n = 14)		CUV (n = 23)		
Location					
Trunk	9	64.3%	21	91.3%	.042
Arms	13	92.9%	18	78.3%	.243
Legs	11	78.6%	21	91.3%	.272
Face/Neck	3	21.4%	6	26.1%	.749
Systemic symptoms	4	28.6%	8	34.8%	.695
Arthritis & arthralgia	1	7.1%	1	4.3%	.715
Edema	1	7.1%	0	0.0%	.194
Fever	0	0.0%	5	21.7%	.061
Angioedema	2	14.3%	1	4.3%	.283
Myalgia	0	0.0%	1	4.3%	.429
Response to treatment					
Anti-histamine taking	13	92.9%	23	100.0%	.194
Response to anti-histamine	5	38.5%	12	52.2%	.429
Colchicine taking	4	28.6%	6	26.1%	.869
Prednisolone taking	10	71.4%	17	73.9%	.869
Indomethacin taking	1	7.1%	2	8.7%	.867
Others					
Cyclosporine	1	7.1%	1	4.3%	.715
Methotrexate	1	7.1%	0	0.0%	.194
Azathioprine	1	7.1%	0	0.0%	.194
Response to overall treatment	10	71.4%	20	87.0%	.242
Time to response (Mean ± S.D) (days)	46.29±58.51		26.52±33.11		.196
Time to improvement (Mean ± S.D) (days)	68.92±82.18		35.13±36.21		.180

Table 4.3 The features of patients in urticarial vasculitis group (UV) and patients in compatible with urticarial vasculitis group (POS) (Cont)

	UV vs CUV				p-value
	UV (n = 14)		CUV (n = 23)		
Relapse	3	21.4%	1	4.3%	.105
Laboratory findings					
Complete blood count	10	71.4%	13	56.5%	
Normal	10	100.0%	9	69.2%	.054
Anemia	0	0.0%	2	15.4%	.194
Leukocytosis	0	0.0%	1	7.7%	.370
Thrombocytopenia	0	0.0%	1	7.7%	.370
ANAs	5	35.7%	11	47.8%	
Negative	3	21.4%	7	17.4%	
Positive	2	40.0%	4	36.4%	.889
Speckled	1	50.0%	2	50.0%	1
Cytoplasm	0	0.0%	1	25.0%	.439
Homogenous	1	7.1%	1	4.3%	.715
Nucleolar	-		-		-
Viral hepatitis profile	4	28.5%	11	47.8%	
Normal	4	100.0%	11	100.0%	-
Creatinine	7	50%	14	60.9%	
Normal	7	100.0%	14	100.0%	.517
ESR	4	28.5%		7 30.4%	
(Mean ± S.D)	46.75±33.10		41.86±36.82		.831
Normal	1	20.0%	1	14.3%	.793
High (>15mm/h in men, or >20mm/h in women)	3	60.0%	6	85.7%	.310
Thyroid function test	3	21.4%	5	21.7%	
Normal	3	100.0%	3	60.0%	.206
Hypothyroidism	0	0.0%	1	20.0%	.408
Hyperthyroidism	0	0.0%	1	20.0%	.408

Table 4.3 The features of patients in urticarial vasculitis group (UV) and patients in compatible with urticarial vasculitis group (POS) (Cont)

	UV vs CUV				p-value
	UV (n = 14)		CUV (n = 23)		
Anti-TG	0	0.0%	1	4.3%	-
Positive	0	0.0%	1	100.0%	
Anti-TPO	0	0.0%	1	4.3%	
Positive	0	0.0%	1	100.0%	-
Liver function test	6	42.9%	11	47.8%	
Normal	6	100.0%	8	72.3%	-
Transaminitis	0	0.0%	3	27.7%	-
Stool examination	0	0.0%	7	30.4%	-
Normal	0	0.0%	7	100.0%	
Urine analysis	5	35.7%	10	43.4%	
Normal	5	100.0%	10	100.0%	-
C3	1	7.1%	3	13%	
Normal	1	100.0%	3	100.0%	-
C4	2	14.2%	3	13%	
Normal	1	50.0%	3	100.0%	-
low	1	50.0%	0	0.0%	-

From histopathologic examinations, the superficial perivascular infiltration and perivascular infiltration patterns were found 100% in both UV and CUV. No difference in the histopathologic patterns was found between the 2 groups.

According to intensity of cell, majority of UV and CUV was grade 1 (42.9%) and grade 2 (56.5%) of cell infiltration, respectively. Grade 3 of cell infiltration was found significantly in UV compare to CUV ($p<0.05$).

The dermal edema is similar between the 2 groups. The fibrinoid deposition in vessel wall and vessel wall damage were found only in the UV, while none of the patients in CUV had these findings.

No difference in type of cell infiltrations was found in both groups.

Table 4.4 The histopathologic examinations in urticarial vasculitis group (UV) and compatible with urticarial vasculitis group (CUV)

	UV vs CUV				p-value
	UV (n = 14)		CUV (n = 23)		
Superficial infiltrate	14	100.0%	23	100.0%	-
Deep infiltrate	10	71.4%	13	56.5%	.365
Perivascular infiltrate	14	100.0%	23	100.0%	-
Interstitial infiltrate	13	92.9%	19	82.6%	.377
Intensity of cell infiltrate					
Grade 1 (<25%)	6	42.9%	9	39.1%	.823
Grade 2 (26-50%)	4	28.6%	13	56.5%	.098
Grade 3 (51-75%)	4	28.6%	1	4.3%	.037
Grade 4 (>75%)	0	0.0%	0	0.0%	-
Dermal edema	4	28.6%	4	17.4%	.423
Fibrinoid deposit at vessel wall	7	50.0%	0	0.0%	-
Vessel wall damaged	12	85.7%	0	0.0%	-
Nuclear dust	12	85.7%	11	47.8%	.021
Extravasated RBC	9	64.3%	16	69.6%	.739
Fibrin thrombi in blood vessel	3	21.4%	0	0.0%	.021
Neutrophilic infiltrate					
0%	1	7.1%	4	17.4%	.377
1-25%	3	21.4%	10	43.5%	.173
26-50%	5	35.7%	7	30.4%	.739
51-75%	3	21.4%	2	8.7%	.272
76-100%	2	14.3%	0	0.0%	.062
Lymphocytic infiltrate					
0%	-		-		-
1-25%	3	21.4%	2	8.7%	.272
26-50%	6	42.9%	3	13.0%	.040
51-75%	2	14.3%	10	43.5%	.066
76-100%	3	21.4%	8	34.8%	.389

Table 4.4 The histopathologic examinations in urticarial vasculitis group (UV) and compatible with urticarial vasculitis group (CUV) (Cont)

	UV vs CUV				p-value
	UV (n = 14)		CUV (n = 23)		
Eosinophilic infiltrate					
0%	4	28.6%	3	13.0%	.242
1-25%	10	71.4%	15	65.2%	.695
26-50%	0	0.0%	3	13.0%	.159
51-75%	0	0.0%	2	8.7%	.257
76-100%	-		-		-

4.3 Differences between compatible urticarial vasculitis group (CUV) and non-vasculitis group (NON)

From table 4.5, 23 out of 59 patients was in CUV and 22 out of 59 patients (37.3%) was in non-vasculitis group. Majority of the patients in both groups were female which mean age 44 and 47 years as shown in table 4.5. No difference in demographic data, clinical manifestations, possible trigger factors and underlying autoimmune diseases between this 2 groups was demonstrated.

According to clinical data, two patients of CUV (8.7%) had underlying autoimmune diseases including autoimmune thyroiditis, and systemic lupus erythematosus as shown in table 4.5. Two patients of non-vasculitis (9.1%) group had underlying autoimmune diseases including autoimmune thyroiditis, and rheumatoid arthritis. There was no statistic significant in the underlying autoimmune diseases between these 2 groups.

The trigger factors were identified in 30.4% in CUV and 18.2% in non-vasculitis group which was shown no statistic significant (table 4.1).

The mean duration of illness was 28.35±75.18 days in CUV and 74.18±126.86 days in non-vasculitis group. The duration of wheal was 6.26±5.29

days in CUV and 7±12.21 days in non-vasculitis group. These findings showed no statistic significant between the 2 groups.

Majority of CUV had painful symptom (34.8%) when compare to non-vasculitis group (4.5%) which showed statistic different between these 2 groups ($p < 0.05$). The skin lesions presented with plaques and papules and usually located on arms, trunk and face/neck which were similar in both groups.

The systemic symptoms were presented 34.8% in CUV and 9.1% in non-vasculitis group as shown in figure 4.3.

It shows no difference between trigger factors of CUV (30.4%) and non-vasculitis group (18.2%) at 0.05 significant level.

All patients in both groups received anti-histamines. Non-vasculitis group had more response to antihistamine treatment compared to CUV in significant level (81.8% vs 52.2%, $p < 0.05$). The patients in CUV received prednisolone more than the patients in non-vasculitis group which showed statistic significant (73.9% vs 36.4%, $p < 0.05$). No statistic significant was shown in other medications such as colchicine, indomethacin, and cyclosporine.

According to the response to overall treatment, time to response, time to improvement, and relapse, no statistic significant was detected between the 2 groups.

The laboratory data included CBC, ANA, viral hepatitis profile, creatinine, ESR, TFT, Anti-TG Ab, Anti-TPO Ab, Liver function test, urine analysis, C3, and C4. The results were as the follows:

CBC was done in 13 patients in CUV (56.5%) and 16 patients in non-vasculitis group (72.7%). Five patients in CUV had abnormal results as shown in table 4.1.

ANA was done in 11 patients of CUV (47.8%) and 10 patients in non-vasculitis group (45.5%). Four patients of vasculitis group (36.4%) and six patients of non-vasculitis group (18.2%) had positive ANA test. There was no statistical significance between 2 groups.

Viral Hepatitis Profile was done in 11 patients of CUV (47.8%) and 9 patients of non-vasculitis group. All patients had normal result ($p > 0.05$).

Creatinine was done in 14 patients of CUV (60.8%) and 13 patients of non-vasculitis group (59%)**.** All patients had normal result ($p > 0.05$).

ESR was done in 7 patients of CUV (30.4%) and 3 patients in non-vasculitis group (13.6%). Only 6 patients in CUV (85.7%) had high ESR titer which showed significant between the 2 groups ($p<0.05$). Nevertheless, there was no statistic significant detected in mean of ESR level.

Thyroid function test was done in 5 patients of CUV (21.7%) and 7 patients in non-vasculitis group (31.8%). In CUV, 1 patient had hyperthyroidism (20%) and 1 patient had hypothyroidism (20%). All patients in non-vasculitis group has normal thyroid function test. One patient in CUV with hyperthyroidism were positive for anti-TG and anti-TPO, while non-vasculitis group has 2 patients of positive anti-TG. There was no statistical significance between 2 groups.

Liver function test was done in 11 patients of CUV (47.8%) and 10 patients in non-vasculitis group (45.5%). Three patients in CUV and 2 patients in non-vasculitis group had transminitis.

Stool examination was done only in 7 patients of CUV (30.4%), 3 patients of non-vasculitis group. All of them had normal result.

urine analysis was done in 10 patients of CUV (43.5%) and 10 patients of non-vasculitis group (45.5%). All of them had normal result.

C3 and C4 complement were done only in 3 patients of CUV (13%), and all were normal.

From histopathologic examination between patients with CUV and patients with non-vasculitis group, all of patients showed superficial infiltration. Fifty-six-point-five percent of CUV and 45.5% of non-vasculitis group took deep infiltration. A hundred percent of CUV and 95.5% of non-vasculitis group showed perivascular infiltration. However, majority of CUV (82.6%) had interstitial infiltration, while only 45.5% of non-vasculitis group had this pattern ($p < 0.05$).

According to intensity of cell, majority of non-vasculitis group presented grade 1 infiltration (77.3%) and grade 2 infiltration (22.7%) without grade 3 infiltration. The CUV presented all patterns included grade 1, 2 and 3 in 39.1%, 56.5% and 4.3%, respectively. Dermal edema was not difference in both groups which was found in 4 patients (17.4%) of CUV and 2 patients (9.1%) of non-vasculitis group. From CUV, it found 47.8% had nuclear dust, 69.6% had extravasated RBC. Nevertheless, none of the patients in non-vasculitis group presented all of these features.

Depending on the types of inflammatory cells infiltrations, CUV had all types of cells were seen in both groups. Nevertheless, majority of the patients in non-vasculitis group had no neutophils which showed statistic significant compare to vasculitis group (table 2).

Table 4.5 The features of patients with compatible with urticarial vasculitis group (CUV) and patients with non-vasculitis group (NON)

	CUV vs NON				p-value
	CUV (n = 23)		NON (n = 22)		
Demographic data					
Gender					
Male	6	26.1%	3	13.6%	.297
Female	17	73.9%	19	86.4%	
Age (Mean ± S.D) [range] (years)	44.39±18.67 [23-81]		46.68±17.34 [7-74]		.672
Clinical data					
Trigger factors	7	30.4%	4	18.2%	.339
Drug	2	8.7%	1	4.5%	.317
Herb	0	0.0%	2	9.1%	.139
Seafood	2	8.7%	1	4.5%	.577
Tetanus toxin	1	4.3%	0	0.0%	.323
Exercise	-		-		-
Glutathione capsule	1	4.3%	0	0.0%	.323
Infection	1	4.3%	0	0.0%	.323
Underlying autoimmune	2	8.7%	2	9.1%	.963
Autoimmune thyroiditis	1	4.3%	1	4.5%	.974
System lupus erythematosus	1	4.3%	0	0.0%	.323
Rheumatoid arthritis	0	0.0%	1	4.5%	.301
Duration of illness (Mean ± S.D) (days)	28.35±75.18		74.18±126.86		.152
Skin lesion					

Table 4.5 The features of patients with compatible with urticarial vasculitis group (CUV) and patients with non-vasculitis group (NON) (Cont)

	CUV vs NON				p-value
	CUV (n = 23)		NON (n = 22)		
Duration of wheal (Mean ± S.D) (days)	6.26±5.29		7±12.21		.792
Painful	8	34.8%	1	4.5%	.011
Plaques	23	100.0%	22	100.0%	-
Papules	4	17.4%	3	13.6%	.728
Location					
Trunk	21	91.3%	14	63.6%	.026
Arms	18	78.3%	16	72.7%	.666
Legs	21	91.3%	18	81.8%	.349
Face/Neck	6	26.1%	4	18.2%	.524
Systemic symptoms	8	34.8%	2	9.1%	.038
Arthritis & arthralgia	1	4.3%	1	4.5%	.974
Edema	-		-		-
Fever	5	21.7%	2	9.1%	.242
Angioedema	1	4.3%	0	0.0%	.323
Myalgia	1	4.3%	0	0.0%	.323
Response to treatment					
Anti-histamine taking	23	100.0%	22	100.0%	-
Response to anti-histamine	12	52.2%	18	81.8%	.035
Colchicine taking	6	26.1%	8	36.4%	.457
Prednisolone taking	17	73.9%	8	36.4%	.011
Indomethacin taking	2	8.7%	4	18.2%	.349
Others					
Cyclosporine	1	4.3%	0	0.0%	.323
Response to overall treatment	20	87.0%	19	86.4%	.953
Time to response (Mean ± S.D) (days)	26.52±33.11		16.14±14.68		.184

Table 4.5 The features of patients with compatible with urticarial vasculitis group (CUV) and patients with non-vasculitis group (NON) (Cont)

	CUV vs NON				p-value
	CUV (n = 23)		NON (n = 22)		
Time to improvement (Mean ± S.D) (days)	35.13±36.21		32.8±53.95		.867
Relapse	1	4.3%	1	4.5%	.974
Laboratory findings					
Complete blood count:	13	56.5%	16	72.7%	
Normal	9	69.2%	16	100.0%	.017
Anemia	2	15.4%	0	0.0%	.104
Leukocytosis	1	7.7%	0	0.0%	.259
Thrombocytopenia	1	7.7%	0	0.0%	.259
ANAs	11	47.8%	10	45.5%	
Negative	7	30.4%	4	18.2%	
Positive	4	36.4%	6	60.0%	.279
Speckled	2	50.0%	5	83.3%	.260
Cytoplasm	1	25.0%	0	0.0%	.197
Homogenous	1	25.0%	0	0.0%	.197
Nucleolar	0	0.0%	2	33.3%	.197
Viral hepatitis profile	11	47.8%	9	40.9%	
Normal	11	100.0%	9	100.0%	-
Creatinine	14	60.8%	13	59.0%	
Normal	14	100.0%	13	100.0%	-
ESR	7	30.4%	3	13.6%	
(Mean ± S.D)	41.86±36.82		15.5±6.36		.368
Normal	1	14.3%	3	100.0%	.023
High	6	85.7%	0	0.0%	.023
Thyroid function test	5	21.7%	7	31.8%	
Normal	3	60.0%	7	100.0%	.067
Hypothyroidism	1	20.0%	0	0.0%	.217

Table 4.5 The features of patients with compatible with urticarial vasculitis group (CUV) and patients with non-vasculitis group (NON) (Cont)

	CUV vs NON				p-value
	CUV (n = 23)		NON (n = 22)		
Hyperthyroidism	1	20.0%	0	0.0%	.217
Anti-TG	1	4.3%	2	9.1%	-
Positive	1	100.0%	2	100.0%	
Anti-TPO	1	4.3%	2	9.1%	
Normal	0	0.0%	2	100.0%	-
Positive	1	100.0%	0	0.0%	-
Liver function test	11	47.8%	10	45.5%	
Normal	8	72.7%	8	80.0%	-
Transaminitis	3	27.3%	2	20.0%	-
Stool examination	7	30.4%	3	13.6%	-
Normal	7	100.0%	3	100.0%	
Urine analysis	10	43.5%	10	45.5%	-
Normal	10	100.0%	10	100.0%	
C3	3	13.0%	0	0.0%	-
Normal	3	100.0%	0	0.0%	
C4	3	13.0%	0	0.0%	
Normal	3	100.0%	0	0.0%	-
low	-		-		-

Table 4.6 The histopathologic examinations in compatible with urticarial vasculitis group (CUV) and non-vasculitis group (NON)

	CUV vs NON				p-value
	CUV (n = 23)		NON (n = 22)		
Superficial infiltrate	23	100.0%	22	100.0%	-
Deep infiltrate	13	56.5%	10	45.5%	.458
Perivascular infiltrate	23	100.0%	21	95.5%	.570
Interstitial infiltrate	19	82.6%	10	45.5%	.009
Intensity of cell infiltrate					
Grade 1 (<25%)	9	39.1%	17	77.3%	.010
Grade 2 (26-50%)	13	56.5%	5	22.7%	.021
Grade 3 (51-75%)	1	4.3%	0	0.0%	.323
Grade 4 (>75%)	0	0.0%	0	0.0%	-
Dermal edema	4	17.4%	2	9.1%	.413
Fibrinoid deposit at vessel wall	-		-		-
Vessel wall damaged	-		-		-
Nuclear dust	11	47.8%	0	0.0%	.000
Extravasated RBC	16	69.6%	0	0.0%	.000
Fibrin thrombi in blood vessel	-		-		-
Neutrophilic infiltrate					
0%	4	17.4%	13	59.1%	.004
1-25%	10	43.5%	7	31.8%	.420
26-50%	7	30.4%	2	9.1%	.074
51-75%	2	8.7%	0	0.0%	.157
76-100%	-		-		-
Lymphocytic infiltrate					
0%	-		-		-
1-25%	2	8.7%	0	0.0%	.157
26-50%	3	13.0%	2	9.1%	.673
51-75%	10	43.5%	2	9.1%	.009
76-100%	8	34.8%	18	81.8%	.001

Table 4.6 The histopathologic examinations in compatible with urticarial vasculitis group (CUV) and non-vasculitis group (NON) (Cont)

	CUV vs NON				p-value
	CUV (n = 23)		NON (n = 22)		
Eosinophilic infiltrate					
0%	3	13.0%	3	13.6%	.953
1-25%	15	65.2%	17	77.3%	.372
26-50%	3	13.0%	1	4.5%	.317
51-75%	2	8.7%	1	4.5%	.577
76-100%	-		-		-

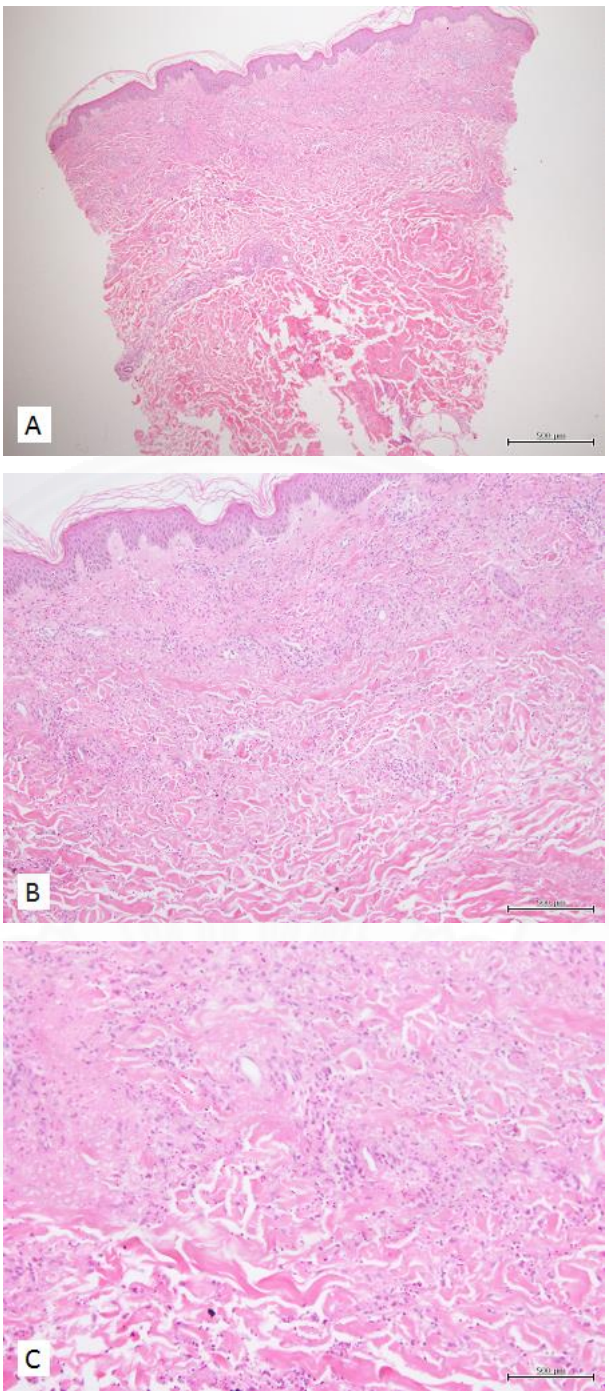

Figure 4.4 Histologic findings in urticarial vasculitis group, code011 (hematoxylin-eosin). A, x40 and B, x100 showing superficial and deep perivascular and interstitial infiltration. C, x200 showing fibrinoid deposition at vessel walls, nuclear dust and RBC extravasation, grade 3 of neutrophils, grade 2 of lymphocytes, and grade 1 of eosinophilic infiltration.

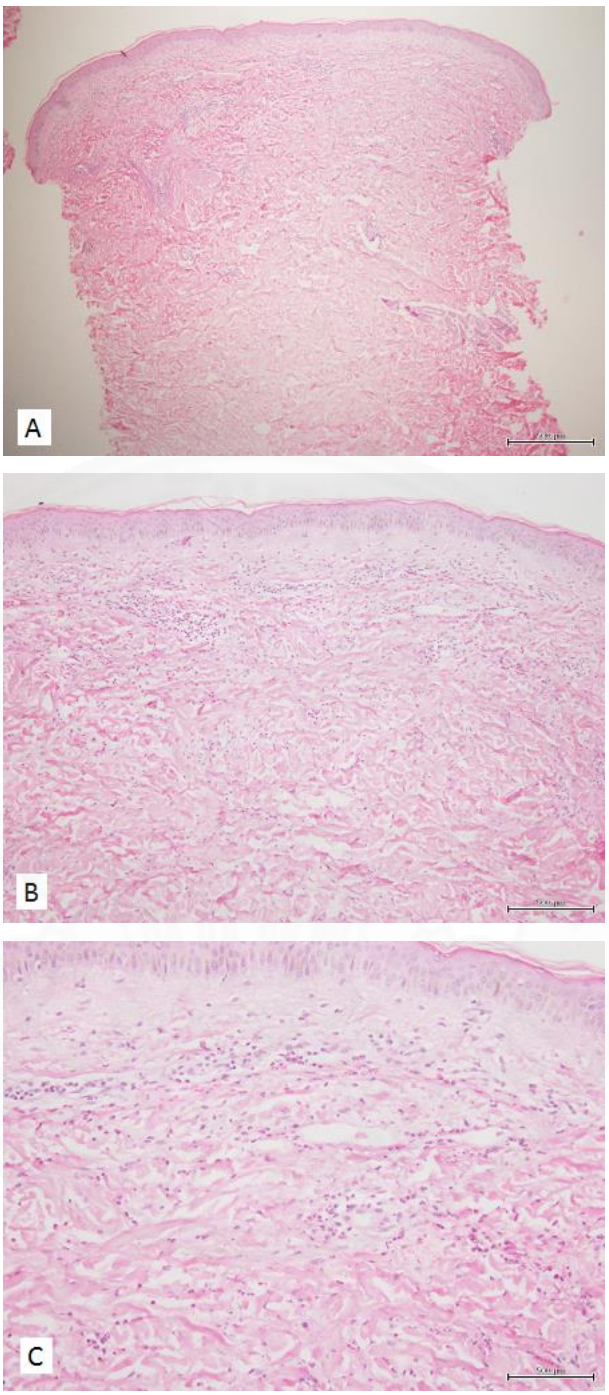

Figure 4.5 Histologic findings in compatible with urticarial vasculitis group, code007 (hematoxylin-eosin). A, x40 and B, x100 showing superficial perivascular and interstitial infiltration. C, x200 showing nuclear dust, grade 2 of neutrophils and lymphocytes, and grade 1 of eosinophilic infiltration.

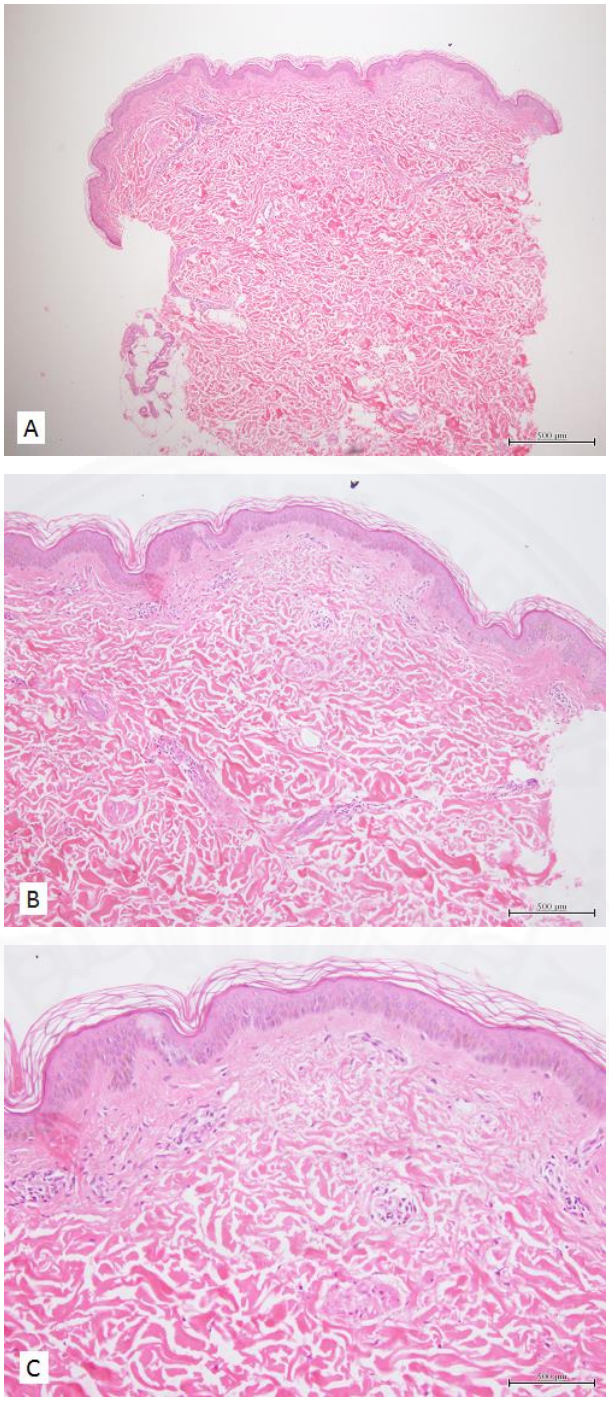

Figure 4.6 Histologic findings in non-vasculitis group, code010 (hematoxylin-eosin). A, x40 and B, x100 showing superficial and deep perivascular and interstitial infiltration. C, x200 showing grade 4 of lymphocytic infiltration and grade 1 of eosinophil infiltration.

CHAPTER 5
DISCUSSION AND RECOMMENDATIONS

5.1 Discussion

Urticarial vasculitis is characterized histologically by small vessel vasculitis in which atypical urticarial lesions. UV is a rare disease but possibly underdiagnosed. The clinical features range from cutaneous manifestations alone to skin lesions accompany with associated systemic symptoms.

In this study, fifty-nine patients who were included by the clinical criteria received histopathologic examinations. All patients were divided into vasculitis group and non-vasculitis group. Vasculitis group (n=37, 62.7%) was divided into 2 groups by histologic criteria (direct or indirect evidence of vasculitis), including “urticarial vasculitis group” (n=14, 23.7%) and “compatible with urticarial vasculitis group” (n=23, 39%). Twenty-two patients that had no signs of vasculitis were classified under “non-vasculitis group” (n=22, 37.2%).

Similar to previous reports, our patient in vasculitis group had more painful or burning urticarial wheals that persist more than 24 hours and resolved with hyper pigmentation when compared to non-vasculitis group. The average durations of wheal were 6.35±5.49 days and the duration of illness were 34.24±73 days in vasculitis group.

Nevertheless, 37.3% of our patients in non-vasculitis group can present with persistent urticarial wheals and resolved with hyperpigmentation. These findings were different from the clinical manifestation of ordinary urticaria which the wheal is not persist and resolves without residual hyperpigmentation (34). However physical urticaria and delay pressure urticaria can present with urticarial wheals last long than 24 hours, but unlikely to have residual hyperpigmentation in classic case (45).

The hyperpigmentation can be explained in ordinary urticaria by scratching (48). Mieko OI et al reported 5 cases of acute urticaria with the lesions persisted more than 24 hours and resolved with purpura (46). Moreover, all of these

cases were associated with bacterial infections (acute cholecystitis, upper respiratory tract infection, cellulitis and dental carries) (46).

UV represented a clinical spectrum of disease ranging from cutaneous manifestation alone to systemic manifestations. Twelve patients in vasculitis group (32.4%) had associated systemic symptoms which were fever (13.5%), arthritis or arthralgia (5.4%), angioedema (8.1%), edema (2.7%), and myalgia (2.7%). The patients in vasculitis group had these manifestations more number than the non-vasculitis group which was shown statistic significant.

Less number systemic symptoms were found in our study compare to previous reports. (4,27,28) Prior studies reported the systemic symptoms in UV patients around 50-60% which arthralgia was the most common systemic manifestations (4,27,28).

Variable of systemic diseases have been reported to associated with UV included connective tissue diseases such as SLE, Sjogren's syndrome, autoimmune thyroiditis, malignancy such as IgA myeloma, and infection such as hepatitis B or C, Epstein-Barr virus and Coxackie (1,33). Other physical factors including ultraviolet light, cold exposure or exercise have been reported as aggregating factors in UV (1).

Approximately 10% of UV patients had SLE from the study of Mehregan DR et al., and Dincy et al. (4,27). Dincy et al. also reported 17.6% had juvenile rheumatoid arthritis, 14.7% had thyroid dysfunction and 1.5% had autoimmune hepatitis (27).

In our study only 10.8% of vasculitis group had underlying autoimmune disease which were 1.7% of SLE. This showed less number of UV patient associated with SLE and rheumatoid arthritis compared to previous reports (4,27). Our study reported 5.4% of autoimmune thyroiditis, and 2.7% of rheumatoid arthritis. These findings also supported previous study that UV associated with rheumatoid arthritis and autoimmune thyroiditis but less number of rheumatoid arthritis than the study of Dincy et al. (33,27).

Majority of the patients in vasculitis group (75.6%) had no trigger factor. The possible aggregating factors were found in 9 patients (24.3%) which were medications in 5 patients, exercise in 1 patient, food in1patient and infection in 1 patient as shown in table 4.1.

As the previous reports, UV may occur following the medications such as penicillin, cephalosporin, sulfonamide, phenytoin, thiazide and allopurinol and exercise (28). Y. Kano et al. presented the expression of E-selectin and VCAM-1with the appearance of eosinophils in the urticarial lesions after physical exercise (31).

Most of the patients in our study received antihistamines. The response was 81.8% of the patients in non-vasculitis group and 47.2% of the patients in vasculitis which was showed statistic significant.

Venzor et al. (1) found that antihistamines could not control the inflammation due to immune complex deposition in the patient of urticarial vasculitis and could not alter the progression of the symptoms. Antihistamines can be used along with other drugs for controlling the itching symptom. This finding supports the response to antihistamine from our study which showed more response in non-vasculitis group.

No statistic significant was shown among abnormal laboratory results in both groups. A high ESR level was the most common abnormal finding which found significantly more number in vasculitis group compared to non-vasculitis group. Since increase ESR level was induced by inflammation both infectious and non-infectious causes (47). More inflammation in UV patients may be explained the association with increase ESR level compared to ordinary urticaria.

Our study defined ESR level > 20 mm/h as high level. We found this is the only laboratory finding that differ between vasculitis and non-vasculitis group. Therefore in the patients with high ESR level, the patients are more likely to have vasculitis than ordinary urticaria.

Other laboratory investigations were shown no statistic significant between vasculitis and non-vasculitis group. Nevertheless, the investigations still have benefit for discovering the underlying causes.

From the clinical findings in our study, there were no different in pain symptom, systemic symptoms and the response to antihistamine between UV and CUV group. Additionally, no difference in abnormal laboratory results including ESR level we're found between these groups. This can support the CUV was the subset of UV.

Concerning the histologic findings, all the patients in vasculitis group had superficial infiltrate while 62.2% had deep infiltrate. All the patients in vasculitis group and 95.5% of the patients in non-vasculitis group had perivascular infiltrate. Eighty-six-point-five percent in vasculitis group had interstitial infiltrate which showed statistic significant compared to only 45.5% in non-vasculitis group. Most of the patients in vasculitis group had moderated intensity of inflammatory cells infiltration (45.9%), followed by mild (40.5%) and dense (13.5%) intensity of cells respectively. Dermal edema was similar between vasculitis and non-vasculitis group.

In vasculitis group, majority of the type of inflammatory cells was mixed cell infiltration composed of lymphocyte that was found 100% which mostly had grade 3 to 4 intensity, neutrophil that was found 86.4% which had mostly grade 1 to 2 intensity, and eosinophil that was found 81.8% which mostly had grade 1 intensity.

In contrast to non-vasculitis group, the majority of inflammatory cells infiltration was lymphocytes which had grade 1 intensity, followed by eosinophils and none of them had neutrophils infiltration.

There were studies reported lymphocytic vasculitis (36) or perivascular mixed cell infiltrate (13,21) in patients exhibiting clinical of UV. These findings can be explained by the dynamic of cell infiltrate in leukocytoclastic vasculitis that can change from neutrophil-predominate infiltrate to mononuclear-predominate cell infiltrate at 48 hours of lesion (43). Therefore, the cell type infiltrate should not be in the important criteria for diagnosis of UV.

In our study, the histological criteria in CUV group included the presence of nuclear dusts or extravasation of red blood cells with perivascular inflammatory cells infiltrate. From the clinical and laboratory findings as mention above, we assume that the CUV was the subset of UV. The histological findings were similar to the previous report. J. Andrew et al. reported the histological criteria in early UV which had subtle change of perivascular nuclear debris (leukocytoclasis) without fibrin deposits and obvious vascular wall damage as CUV group in our study (35).

There are some limitations in our study. As this was a retrospective review of the medical records and histopathologic examination. There was a potential of having incomplete data in both clinical findings and for laboratory results.

5.2 Recommendations

More number of UV patients and multicenter study should be done in the future. As this multicenter study can represent the incident, clinical findings and disease course of the UV patients in Thailand.

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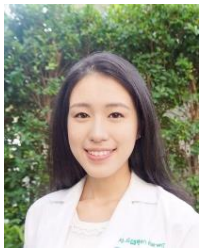
BIOGRAPHY



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