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Urticarial Vasculitis: Etiologies and Clinical Course

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SUMMARY Out of 64 patients diagnosed with urticarial vasculitis (UV), 49 (76.6%) presented with their first attack of UV. The others experienced recurrent attacks with a mean number of 3.3 past recurrences. Fifteen patients had angioedema (23.4%) and 16 (25%) suffered systemic involvement. The most common abnormal laboratory finding was an increased erythrocyte sedimentation rate. Six of 62 patients (9.7%) had decreased C3 levels. A cause could be identified in 19 patients (29.7%). The most common identified cause was infection; other causes included drugs, malignancy and systemic lupus erythematosus (SLE). The prevalence of immunoreactant deposits in the skin lesions measured by DIF was 54.7% (35 of 64 patients). The median disease duration of each episode was 85 days. The probability that patients were free of symptoms within one year was 70%. Patients with an idiopathic cause had a statistically significant longer course duration of each episode than the group with upper respiratory tract infection. Compared to reports from Western countries, our patients seemed to have less severe symptoms and a lower percentage of hypocomplementemic UV and SLE.

Chronic urticaria and angioedema may be manifestations of an underlying cutaneous necrotizing venulitis. Urticarial vasculitis (UV) is characterized by pruritic, burning or painfully raised, superficial, erythematous or edematous, circumscribed wheals with foci of purpura and induration. The individual urticarial lesions last frequently more than 24 hours and leave a residual transient hyperpigmentation.[1] Associated features include fever, malaise, myalgia and specific organ involvement. The episodes of urticaria are recurrent, and their duration ranges from months to years. Sometimes, the lesions may be indistinguishable from those of chronic urticaria without vasculitis on the basis of history and clinical appearance. Previous studies reported immunogenetic differences between Asian and Caucasian patients causing different clinical presentations as well as influencing the frequency of autoantibodies in some autoimmune diseases.[2,3] As most of the studies involving UV originated from Western countries, it was our goal to provide information on the clinical features of Asian patients with UV. Thus this study aimed to report the etiologies, clinical features and outcome of UV in a university hospital in Thailand.

MATERIALS AND METHODS

The records of patients with UV who attended the Department of Dermatology, Siriraj Hospital, Mahidol University, between January 2006 and December 2007 were retrospectively reviewed. Pa-

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tients aged at least 18 years who fulfilled the following criteria were diagnosed as UV: a crop of urticarial wheals with individual lesions lasting more than 24 hours or wheals that healed with residual hyperpigmentation which showed evidence of leukocytoclastic vasculitis in their lesional skin biopsies (swelling of endothelial cells, a predominant polymorphonuclear neutrophilic perivascular infiltration, leukocytoclasis, extravasation of red blood cells, and fibrinoid deposits in and around the blood vessel walls) were enrolled. The study was approved by the Ethics Committee on Research Involving Human Subjects of Siriraj Hospital, Mahidol University.

Demographic data, etiologies, clinical features, the disease courses, treatment and outcome were studied. Laboratory investigations included complete blood counts (CBC), erythrocyte sedimentary rate (ESR), urinalysis, stool examination and other investigations as necessary for the individual patients, i.e. BUN, creatinine, AST, ALT, ALP, bilirubin, total protein, albumin, HbsAg, anti HCV and anti HIV antibodies, antinuclear antibodies (ANA; by indirect immunofluorescence using rat liver as a substrate), cryoglobulins, serum complement levels (radial immunodiffusion), and chest X-ray.

The lesional skin biopsy specimens were cut into two pieces. One half was rapidly frozen in liquid nitrogen for direct immunofluorescence (DIF), and the other half was studied by routine light microscopy (hematoxylin and eosin). The DIF studies of the skin lesions were performed as previously described.[4] Briefly, the skin biopsy specimens were embedded in Cryomatrix embedding medium (SHANDON, USA) and snap frozen at -70° C until sectioned. The frozen sections were cut 4 μm thick on a cryostat, air-dried, washed twice with phosphate-buffered saline (PBS), pH 7.4 for 10 minutes and then overlaid for 30 minutes with fluorescein isothiocyanate-conjugated rabbit antihuman IgG, IgA, IgM, C3 and fibrin (DAKO patt., Denmark). Thereafter, the section slides were incubated in a humidified chamber at room temperature, washed twice with PBS for 10 minutes and mounted with a medium before viewing with a fluorescence microscope. The DIF patterns were interpreted according to standard criteria.[5] A specimen was considered positive if there was a granular deposit of one or more of the conjugates (IgG, IgA, IgM or C3) at the blood vessel walls and/or along the dermo-epidermal junction (DEJ).

Statistical analyses

All statistical analyses were two-sided at a 95% confidence level using SPSS version 10 for Windows. The *t*-test, Kruskal Wallis test and chi-squared test were used for statistical analysis among continuous (non-normality) and categorical data. A p-value < 0.05 was considered statistically significant. Descriptive statistics *e.g.* mean, median, minimum, maximum, frequency and percentages were used to describe the demographic data, possible causes and laboratory findings. Because some patients were lost to follow up, the Kaplan-Meier survival curve was applied to determine the probability of symptoms resolving at each time point, which showed the probability of remission.

RESULTS

Sixty four patients were enrolled in the study out of which 54 (84.4%) were female. The mean (SD) age of the patients was 37.3 (14.2) years with an age range of 18 to 77 years. The patients who experienced their first UV attack was 76.6%. The others had recurrent attacks. The mean attack recurrence was 3.3 times (range 2-10). Among the patients with recurrent attacks, the average median time interval between each episode was 91 days. The mean duration of each episode, the systemic symptoms and the laboratory data of the patients with recurrent attacks were not statistically significantly different from those of the patients with the first or isolate episode of UV. Nine out of 62 patients (14%) had associated atopic diseases, the most common of which was allergic rhinitis.

Table 1 shows the clinical features of the patients with UV. The most common cutaneous lesion was an erythematous wheal which persisted longer than 24 hours. Residual hyperpigmentation was found in most cases. Common cutaneous symptoms included pruritus, and painful and burning sensations. Angioedema was detected in one fourth of the patients. Sixteen patients (25%) had systemic involvement, mainly fever and arthralgia. Patients with angioedema had a tendency to more systemic

Table 1 Clinical features of our patients with urticarial vasculitis (n = 64)

Clinical features	No.	%
Wheal > 24 hours	60	93.8
Residual hyperpigmentation	53	82.8
Pruritus	47	73.4
Pain	28	43.8
Burning sensation	12	18.8
Angioedema	15	23.4
Systemic involvement	16	25
Fever	7	10.9
Arthralgia	6	9.4
Arthritis	2	3.1
Abdominal pain	2	3.1
Chronic obstructive pulmonary disease	1	1.6
Uveitis	1	1.6
Headache	1	1.6
Nausea, vomiting	1	1.6

Table 2 Abnormal laboratory findings in the patients with urticarial vasculitis

Abnormal parameters	Patients		
	No. (cases)	**No. tested**	**%**
Positive ANA (> 1:40)	7	64	10.9
Increased ESR (> 20 mm/hour)	27	43	62.8
Abnormal CBC	21	64	32.8
Anemia (Hb < 12 gm/dl)	11	64	17.2
Leukocytosis (> 11,000 cells/mm^3)	7	64	10.9
Eosinophilia (> 1,500 cells/mm^3)	1	64	1.6
Thombocytopenia (< 100,000 cells/mm^3)	1	64	1.6
Abnormal urinalysis	4	59	6.8
Abnormal stool examination	1	21	4.8
Decreased C3 level (< 90 mg/dl)	6	62	9.7
Positive HIV antibody	1	11	9.1
Positive Anti-HCV antibody	1	23	4.3
Positive VDRL	1	16	6.3
Positive HBsAg	0	33	0.0

involvement, especially fever, than those without angioedema; however, the difference was not statistically significant ($p = 0.012$). There were also no statistically significant differences among the laboratory parameters, including serum complement, of both groups.

Table 2 shows the abnormal laboratory findings. The most common abnormal laboratory finding was an increased ESR (27 of 43 cases; 62.8%), followed by an abnormal CBC (21 of 64 cases; 32.8%), i.e. mild anemia (11 of 64 cases, 17.2%) and leukocytosis (7 of 64 cases, 10.9%). A positive

Table 3 Possible causes and conditions associated with urticarial vasculitis

Causes/associated conditions	No. of patients (n = 64)	%
Idiopathic	**45**	**70.3**
Infections	**8**	**12.5**
URI	6	9.3
HIV	1	1.6
Syphilis	1	1.6
Drug-induced	**5**	**7.8**
NSAIDs	3	4.7
Antibiotic	1	1.6
Interferon	1	1.6
Malignancies	**5**	**7.8**
CA breast	1	1.6
CA ovary	1	1.6
CA thyroid	1	1.6
CA colon	1	1.6
Pituitary tumor	1	1.6
Systemic lupus erythematosus (SLE)	**1**	**1.6**

Table 4 Direct immunofluorescence findings

Immunoreactant	No. of patients (n = 64)	Site of immunoreactant deposits		
		DEJ only (cases)	**BV only** (cases)	**DEJ & BV** (cases)
IgG	1	0	0	1
IgM	18	1	15	2
IgA	1	0	1	0
C3	30	5	15	10
Total positive cases*	35 (54.7%)			

DEJ, dermo-epidermal junction; BV, blood vessel; *more than one type of immunoreactant could be detected at all locations.

ANA titer of ≥ 1:40 was found in 7 of 64 cases (10.9%) but only one of them, with a titer of 1:2,560 (homogeneous pattern), was diagnosed as systemic lupus erythematosus (SLE). Mild abnormal urinalysis, mostly transient proteinuria was detected in 4 patients (6.8%). Six of 62 patients (9.7%) had a decreased C3 level. One of 11 patients (11%) who were tested for HIV antibody, showed a positive result, and one of 23 patients (4.3%) was positive for anti-HCV antibody. One of 21 patients (4.8%) had an abnormal stool examination (*Blastocystis hominis* infestation). After treatment, the UV symptoms exhibited remission within 3 months. None of the patients was positive for serum HBsAg.

Table 3 shows the possible causes of UV. In forty-five patients (70.3%) a cause could not be identified. The most common identified cause was infection (8 patients, 12.5%), of which upper respiratory tract infection (URI) was the most common one. Other causes included drugs (5 patients, 7.8%), malignancy (5 patients, 7.8%), and SLE (1 patient, 1.6%). The culprit drugs were non-steroidal anti-inflammatory drugs (ponstan and naproxen), antibi-

Table 5 Clinical courses according to the etiologies

Causes	No. of patients	Duration of each episode (days)		Total duration until remission (days)***	
		Median	Range	Median	Range
Unknown	45	91	14-3575	119.5	14-3,897
Infections*	8	23	12-394	46.5	12-800
URI	6	16	12-34	16	12-410
HIV	1	394	394	800	800
Syphilis	1	85	85	85	85
Malignancies**	5	21	15-25	177	15-688
Drugs	5	59	10-743	59	10-743
SLE	1	42	42	42	42

* and **, significantly different compared to idiopathic disease at p value < 0.05; ***, including every episode of each patient

Table 6 Comparison of disease characteristics of previous studies with our data

Characteristics	Sanchez *et al.*[7] (n = 40)	Mehregan *et al.*[6] (n = 72)	Davis *et al.*[9] (n = 132)	Our study (n = 64)
	Cases (%)			
Hypocomplementemic UV	16 (40)	23 (32)	24 (18.2)	6 (9.7)
SLE	N/A*	8 (11.1)	15 (11.4)	1 (1.6)
ANA positive	N/A	16/69 (23.2)	43/121 (35.5)	7/64 (10.9)
Systemic symptoms				16 (25)
- Fever	6 (15)	4 (5.5)	15 (11.4)	7 (10.9)
- Arthralgia	21 (52.5)	39 (54.2)	44/132	6 (9.4)
- Arthritis	11 (27.5)	N/A	(33.3)	2 (3.1)
- Abdominal pain or chest pain	10 (25)	15 (20.8)	N/A	2 (3.1)
- COPD/asthma	7 (17.5)	9 (12.5)	9 (6.8)	1 (1.6)
- Nausea/vomiting	9 (22.5)	N/A	N/A	1 (1.6)
- Uveitis, episcleritis	7 (17.5)	N/A	5 (3.8)	1 (1.6)
- Headache	N/A	N/A	N/A	1 (1.6)
- Neurological symptoms	3 (7.5)	N/A	2 (1.5)	-
- Renal disease	14 (35)	4 (5.5)	3 (2.3)	-
- Cardiac symptoms	1 (2.5)	N/A	N/A	-

*, not available

otics and interferon. UV ccurred within 3 to 10 days of taking the drugs. After the responsible drugs were withdrawn, the symptoms disappeared within 21 days. In most patients with malignancy, UV occurred within one year after the malignancy had been detected.

Concerning the interval between the first day of the URI symptoms and the onset of UV, half of the patients noted the URI symptoms at a mean of 5 days prior to the onset of the UV symptoms (range 4-6 days). The remission of the URI symptoms occurred at a mean of 9 days (range 7-16 days) before the remission of the UV symptoms.

Table 4 shows the DIF findings in our patients. Deposits of immunoreactants at the blood vessel walls and/or along the DEJ were detected in 35 of 64 cases (54.7%). C3 was the most common immunoreactant deposit, followed by IgM.

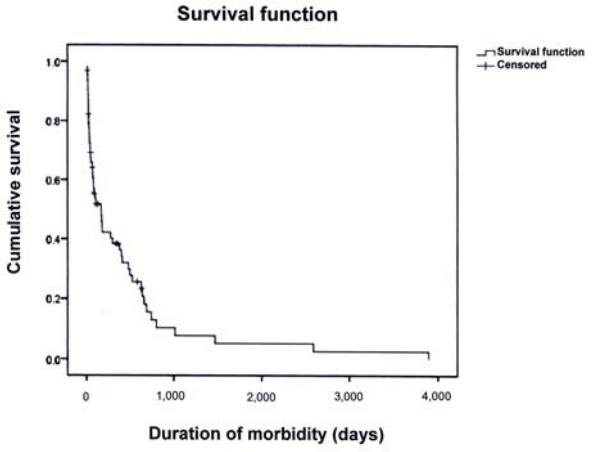

Fig. 1 A Kaplan-Meier survival curve demonstrating the total disease duration in patients with urticarial vasculitis (n = 64). In half of the patients the UV resolved completely within 164 days. The probability that patients were free of symptoms after one year from the onset was 65%.

After treatment, half of the patients experienced remission of the symptoms within 33 days and 80% of the patients had remission of the symptoms within 6 months. The treatment included oral antihistamines (68.8%), colchicines (65.6%), NSAIDs (42.2%) and systemic corticosteroids (40.6%).

The median disease duration of each episode was 85 days (range 10 to 3,575 days). Three fourth of the patients had complete resolution within 394 days. The probability that patients were free of symptoms within one year was 70%. The mean disease duration of patients with hypocomplementemia was 660 days whereas the mean disease duration of those with normocomplementemia was 222 days ($p < 0.001$).

Table 5 shows the courses of the patients according to the etiologies. Patients with an idiopathic cause had a statistically significant longer course duration of each episode than those with infection, especially URI, as well as those with malignancy. One patient with drug-induced UV had taken the culprit drug for treating dysmenorrhea every month for more than 2 years.

Table 6 compares the disease characteristics of previous studies with our data. Our patients seemed to have a lower percentage of HUV and SLE and less systemic symptoms.

DISCUSSION

Similar to previous studies,[6,7] there was a higher prevalence of UV among females. Erythematous wheals which persisted longer than 24 hours with residual hyperpigmentation were found in most cases. The common cutaneous symptoms in this study were pruritus and painful and burning sensations. No patient had photosensitivity in contrast to the studies of Dincy *et al.*[8] and Davis *et al.*,[9] which reported the occurrence of photosensitivity as 14.7% and 2.27%, respectively.

In the present study, 14% of the patients had associated atopic diseases. Vichyanond *et al.*[10] reported the prevalence of allergic rhinitis and asthma in Thai university students at 26.3% and 8.8%, respectively. This implies that there was no increased prevalence of atopy in our UV patients.

Extracutaneous manifestations of UV were commonly reported and were often associated with a decrease in serum hemolytic complement activity. In our study, the prevalence of hypocomplementemic UV (HUV) was low (9.7%) in comparison to the previous reports which documented 20.6% to 64%.[6, 8, 11, 12] Most of our patients had a benign course. The most common systemic involvements in our patients were constitutional symptoms such as fever and arthralgia. Chronic obstructive pulmonary disease (COPD) was detected in only one patient (1.6%). COPD was previously reported in 20-30% of patients with UV.[13] Lung biopsies revealed leukocytoclastic vasculitis.[14] HUV may represent a subset of patients with SLE with shared clinical manifestations, laboratory and immunological factors.[15,16] Mehregan *et al.*[6] reported that 11% of their 72 cases with UV were diagnosed as SLE. However, only one case of SLE (1.6%) was detected in the present study.

UV may be associated with other systemic diseases or causes (secondary UV) or it may be idiopathic. Most patients with NUV are idiopathic.[17] Systemic diseases associated with UV include serum sickness, SLE, Sjogren's syndrome, infection with

hepatitis A, B or C, or Epstein-Barr virus, neoplasias, IgG or IgM gammopathy, ultraviolet light or cold exposure, exercise, Wegener's granulomatosis, polyarthritis nodosa, Henoch-Schonlein purpura, adverse drug-reactions, and hereditary and acquired angioedema.[13] In this study, a cause could be identified only in 30% of the patients. The most common identified cause was infection, followed by drugs, malignancy and SLE, respectively.

The prevalence of immunoreactant deposits in the skin lesions of our UV patients as detected by DIF was 54.7%. Our one case of SLE had no renal involvement. The DIF study in this patient revealed IgG deposits at the DEJ. Some previous reports suggested that granular deposition of immunoglobulin along the DEJ in patients with UV seemed to suggest the diagnosis of SLE.[7,18] Davis *et al*.[9] reported that 23 out of 24 (96%) of their patients with HUV syndrome and 1 out of 108 (1%) of patients with NUV had immunoreactant deposits at the DEJ compatible with LE, in addition to vascular deposits. Dincy *et al*.[8] reported immunoreactant deposits at the DEJ in 8 of 10 (60%) patients with HUV and 1 of 3 (33.3%) of those with NUV.

Sanchez *et al*.[7] reported that patients with hypocomplementemia had a more severe clinical course than those with normocomplementemia (NUV). They suggested that UV with systemic involvement should be suspected in female patients with recurrent, uncontrolled urticaria accompanied by arthralgia or arthritis, respiratory distress, abdominal pain and increased ESR.[7] There were also reports of some patients with limited cutaneous disease for years before systemic symptoms developed.[7, 19]

In our study, the disease duration of the group with hypocomplementemia was statistically significantly longer than of the group with normocomplementemia. Even though the disease severity in terms of recurrence, uncontrolled urticaria and systemic involvement seemed to be higher in the group with hypocomplementemia than in the group with normocomplementemia, the difference was not statistically significant. It should be noted that the number of patients with hypocomplementemia in this study was rather small. This study was conducted in the department of Dermatology and patients with more severe disease are perhaps seen more often by rheumatologists or other specialists.

In summary, our study provided an overview of patients with UV who presented to dermatologists, including clinical features, etiologies and courses. Compared with reports from Western countries, our patients seemed to have less severe disease and a lower percentage of HUV and SLE.

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