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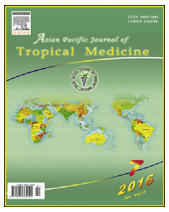

Original research http://dx.doi.org/10.1016/j.apjtm.2016.05.013

Clinical significance of skin rash in dengue fever: A focus on discomfort, complications, and disease outcome

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ARTICLE INFO

Article history:
Received 15 Apr 2016
Received in revised form 16 May 2016
Accepted 23 May 2016
Available online 30 May 2016

Keywords:
Dengue
Exanthema
Pruritus
Serology

ABSTRACT

Objectives: To assess whether the cutaneous features in patients with dengue fever are associated with abnormal blood biochemistry, complications, and poor disease outcome.
Methods: Forty five patients with dengue fever were identified at a medical center in Kaohsiung, Taiwan, from September to November 2014. All cases were exclusively caused by type 1 dengue virus. Patients were classified into two groups, based on the presence or absence of skin rash, and their rash was subclassified into maculopapular, morbilliform, and petechial types. Clinical symptoms, laboratory data, disease outcome, and complications were compared between the two groups.
Results: Thirty two patients with dengue fever developed skin rash (SP group, n = 32) while the rest of 13 did not (SN group, n = 13). The patient numbers in the maculopapular, morbilliform, and petechial group were 4, 21, and 7, respectively. The SP group was younger (P = 0.001), experienced more pruritus (P = 0.008) and more swollen palms/soles (P = 0.015) than the SN group. However, the SN group had greater genital mucosa involvement (P = 0.008), higher platelet transfusion rate (P = 0.003), and lower hemoglobin and hematocrit levels (P = 0.030) than the SP group. Patients with morbilliform lesions had a higher incidence of palm/sole swelling, less genital mucosal involvement, and a lower platelet transfusion rate than did patients with maculopapular or petechial lesions.
Conclusions: Cutaneous manifestations provide an important clue to dengue fever. In patients with dengue fever, those with skin rash tend to have itching and swelling of the palms/soles, however, those without skin rash tend to have more complications and poor disease outcomes.

1. Introduction

Dengue fever (DF) is caused by the dengue virus (DENV), a single-strand RNA flavivirus of the family *Flaviviridae*, a family that also includes the West Nile and yellow fever viruses. The viral etiology of DF has been established since the 1940s [1], and the history of dengue-like diseases can be traced back more than 200 years. The mosquito *Aedes aegypti* is the major vector and the true reservoir for the virus [2].

The incidence of DF has significantly surged in recent years, especially in southern Taiwan during the summer. Globally, approximately 2.5 billion people are estimated to live in dengue-endemic regions, and 50 to 100 million people are infected by dengue virus annually [3]. According to Taiwan Center for Disease Control (CDC), approximately 1 000 to 2 000 people are infected by dengue virus annually [4]. In 2014, Taiwan experienced its large dengue virus outbreak, with the numbers of patients reached record high (>10 000) since 1981 [5].

The typical clinical manifestations of DF vary from self-limited DF to severe dengue hemorrhagic fever and fatal dengue shock syndrome. Most DENV infections are asymptomatic [3]. The classical presentation of mild form of DF includes fever, headache, retro-orbital pain, varied skin rash, myalgia, and arthralgias. In contrast, the severe forms of DF,

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Peer review under responsibility of Hainan Medical College.

including dengue hemorrhagic fever and dengue shock syndrome, are accompanied by thrombocytopenia, and often are fatal.

Previous studies recorded that cutaneous manifestations are present in 65% of patients [6]. A generalized morbilliform rash or a confluent erythematous rash with white islands of sparing petechiae is common [6]. Skin lesions may be the first symptom of DF, and can be helpful for making the diagnosis. However, very few studies have examined the clinical implications, including complications and disease outcomes, of skin rash in patients with DENV infections. In this study, we attempt to compare the differences in laboratory data, disease course, associated symptoms, and treatment prognosis among DF patients with and without skin rash.

2. Materials and methods

2.1. Study population

The prospective study was conducted by the Department of Dermatology at Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan, from September to November 2014. The hospital is a medical facility with 2700 beds that serves as a tertiary referral center in southern Taiwan.

Forty five adult patients 18 years of age or older were enrolled in the study. All patients included in the study had been admitted to the hospital via the hospital's emergency department, and had DENV infection confirmed by laboratory studies. The 45 patients were subsequently divided into 2 groups: (1) those who developed a skin rash (SP group; $n = 32$) and those who did not (SN; $n = 13$). Clinical examination to assess the various cutaneous features was carried out and the relevant investigations, including a battery of serology tests, were done.

2.2. Study criteria

All dengue cases included in this study were confirmed by one of the following criteria: (1) a positive DENV-specific real-time reverse transcription polymerase chain reaction (RT-PCR; QuantiTect SYBR® Green RT-PCR Kit; QIAGEN GmbH, Hilden, Germany); or (2) acute-phase serum positive for DENV-specific non-structural glycoprotein-1 antigen (Bio-Rad Laboratories, Inc, Marnes-la-Coquette, France). These diagnostic tests were performed by Taiwan CDC.

A visual analogue scale (VAS) was used as a subjective evaluation tool to evaluate the degree of pruritus [7]. A VAS is one of the most commonly used methods of assessing the severity of pruritus, and it provides an easy and rapid estimation of itching. Based on detailed analysis from the VAS scores, the extent of pruritus was categorized as: 0, indicating no pruritus, while a VAS score of 10 indicated very severe pruritus. Patients were excluded if they lost follow up and didn't have complete medical records in this hospital.

2.3. Data analysis

SPSS software (Version 17; SPSS, Chicago, IL, USA) was used for statistical analyses. Mean values and standard deviations were performed for all groups. We performed the unpaired Student's *t*-test to evaluate the clinical symptoms, laboratory features, disease outcomes, and complications between the skin rash group (SP group) and control group (SN group). Analysis of variance (ANOVA) and post-hoc analysis were done to evaluate the clinical symptoms, complications and disease outcomes concerning all group differences, and subsequently for further group–group differences between different skin rash types. Significance was defined as a P-value <0.05, with a two-tailed test.

3. Results

3.1. Demographic data, clinical symptoms, and disease outcome in SP and SN groups

The SP group was younger, had higher VAS scores, and had a higher percentage of palm/sole swelling than the SN group. However, they had less genital mucosal involvement and lower platelet transfusion rates compared with the SN group.

A total of 45 Taiwanese patients (19 males and 26 females) were enrolled in this study. All patients had type I DENV [8], confirmed by the Taiwan CDC. None of the patients had been treated before the diagnosis of DF was made. The demographic data, clinical symptoms, and disease outcome in the SP and SN groups are shown in Table 1. The mean age was (52.87 ± 16.24) years (range: 18–80 years of age), and the SP group was significantly younger than the SN group ($P = 0.001$). All patients had fever as their initial symptom. The interval between the onset of fever to the appearance of skin eruption ranged from 1 to 7 d, with an average interval of 3.9 d. Pruritus, swelling of the palms and soles, and mucosal involvement were also noted.

The average VAS among the SP group (2.06) was significantly higher than that among the SN group (2.06 *vs* 0.28,

Table 1
Demographic data, clinical symptoms, and outcome of DENV infection patients.

Parameters	SP group ($n = 32$)	SN group ($n = 13$)	P
Age (year)	48.46	63.69	0.001*
Males (n, %)	14 (43.75)	5 (38.46)	0.376
Females (n, %)	18 (56.25)	8 (61.54)	0.376
Associated symptoms			
Rash onset after fever (d)	3.91	0	X
Fever duration (d, mean ± SD)	4.52 ± 2.46	2.31 ± 1.90	0.177
Itch (VAS = 1–10, mean ± SD)	2.06 ± 2.26	0.28 ± 1.39	0.008*
Palm/sole swelling (n, %)	13 (40.63)	1 (7.69)	0.015*
Mucosal involvement			
Oral (n, %)	4 (12.50)	0 (0)	0.095
Eye (n, %)	1 (3.12)	0 (0)	0.265
Genital (n, %)	10 (31.25)	8 (61.54)	0.008*
Gastrointestinal (n, %)	3 (9.38)	2 (15.38)	0.306
Dengue hemorrhagic fever (n, %)	4 (12.5)	2 (15.4)	0.406
Hemorrhagic manifestation (n, %)**	14 (43.75)	9 (69.23)	0.063
Platelet transfusion (n, %)	1 (3.16)	4 (30.77)	0.003*
Hospitalization days (d, mean ± SD)	6.48 ± 2.47	7.85 ± 3.87	0.15
Disease course (d, mean ± SD)	9.63 ± 3.62	10.62 ± 3.20	0.25

*A two-tailed $P < 0.05$ was considered statistically significant. **Stool occult blood test was positive or hematuria was revealed urinalysis.

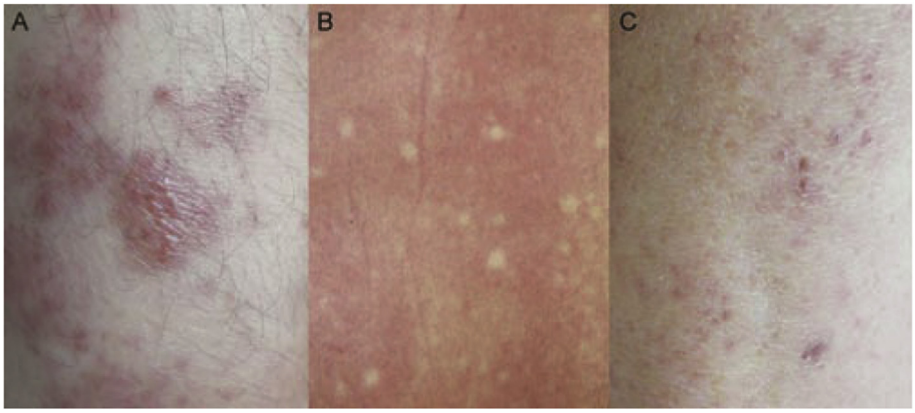

Figure 1. Types of skin manifestations.
(A) maculopapular lesions (B) morbilliform lesions (C) petechial lesions and absence of a rash.

respectively; $P = 0.008$). A significantly greater percentage of patients in the SP group had swollen palms and soles than in the SN group (40.63% *vs* 7.69%, respectively; $P = 0.015$). Furthermore, 58% of the DF patients had mucosal involvement, and thus the incidence of genital mucosal involvement was significantly higher in the SN group ($P = 0.008$). In addition, the SN group also had significantly a higher rate of platelet transfusion (30.77% *vs* 3.16%, respectively; $P = 0.003$). However, there was no correlation between age and platelet transfusion rate ($P = 0.380$).

Fever duration, hospitalization days, and disease courses were similar between the SP and SN group. There was no difference in the duration of fever between the two patient groups (4.52 ± 2.46 in the SP group *vs* 2.31 ± 1.90 in the SN group, respectively; $P = 0.177$). In addition, the percentages of dengue hemorrhagic fever in the SP group (4/32 patients) and the SN group (2/13 patients) were not statistically different. There were no differences in hospitalization days and disease course (from the date of the onset of fever to the discharge day) between the two groups.

3.2. Types of skin manifestations

We categorized skin manifestations into 4 types: maculopapular, morbilliform, petechial, and absence of rash (Figure 1). Of the 45 patients, 32 (71.12%) showed skin manifestations. The skin rash usually spared the face and presented mainly on the limbs, although in some cases the trunk was the predominant site. Patients with the maculopapular type rash were the youngest among the 4 groups.

Patients in the morbilliform rash group had a higher percentage of swollen palms and soles ($P = 0.035$), less genital mucosa involvement ($P = 0.012$), and the lowest platelet transfusion rate ($P = 0.038$) of all 4 categories of skin manifestations. To better investigate the inter-group differences, post-hoc analysis was used. There were no significant differences in rash onset after fever, fever duration, degree of pruritus, dengue hemorrhagic fever presentation, hemorrhagic manifestations, hospitalization days, and disease course between the two groups (Table 2).

Table 2
Demographic data, clinical symptoms, type of lesions and outcome in DENV infection patients.

Parameters	Maculopapular ($n = 4$)	Morbilliforms macule ($n = 21$)	Petechia ($n = 7$)	No skin rash ($n = 13$)	P
Age (year)	46.75	48.76	48.57	63.69	0.036*
Males (n, %)	2 (50.00)	9 (42.86)	3 (42.86)	5 (38.46)	X
Females (n, %)	2 (50.00)	12 (57.14)	4 (57.14)	8 (61.54)	X
Associated symptoms					
Rash onset after fever (d)	4.75	3.86	3.57	0	0.729
Fever duration (d, mean ± SD)	4.00 ± 0.82	5.33 ± 2.80	4.29 ± 1.98	2.31 ± 1.90	0.359
Itch (VAS = 1–10, mean ± SD)	2.25 ± 2.06	1.95 ± 2.22	2.28 ± 2.75	0.38 ± 1.39	0.125
Palm/sole swelling (n, %)	3 (18.8)	10 (62.50)	2 (12.50)	1 (6.30)	0.035*
Mucosa involvement					
Oral	0 (0.00)	4 (100.00)	0 (0.00)	0 (0.00)	0.17
Eye	0 (0.00)	1 (100.00)	0 (0.00)	0 (0.00)	0.76
Genital	3 (16.7)	2 (11.10)	4 (22.20)	9 (50.00)	0.012*
Gastrointestinal	0 (0.00)	2 (9.52)	1 (14.29)	2 (15.38)	0.834
Dengue hemorrhagic fever (n, %)	1 (25.00)	2 (19.00)	1 (14.30)	2 (15.40)	0.852
Hemorrhagic manifestation (n, %)**	3 (75.00)	8 (38.10)	3 (42.86)	9 (69.23)	0.251
Platelet transfusion (n, %)	0 (0.0)	0 (0.00)	1 (14.29)	4 (30.77)	0.038*
Hospitalization days (d, mean ± SD)	7.00 ± 1.15	6.43 ± 2.91	6.86 ± 3.93	7.85 ± 3.87	0.686
Disease course (d, mean ± SD)	10.75 ± 2.06	9.90 ± 2.83	9.57 ± 4.72	10.62 ± 3.20	0.861

*$P < 0.05$ was considered statistically significant. **Stool occult blood test was positive or hematuria was revealed on urinalysis.

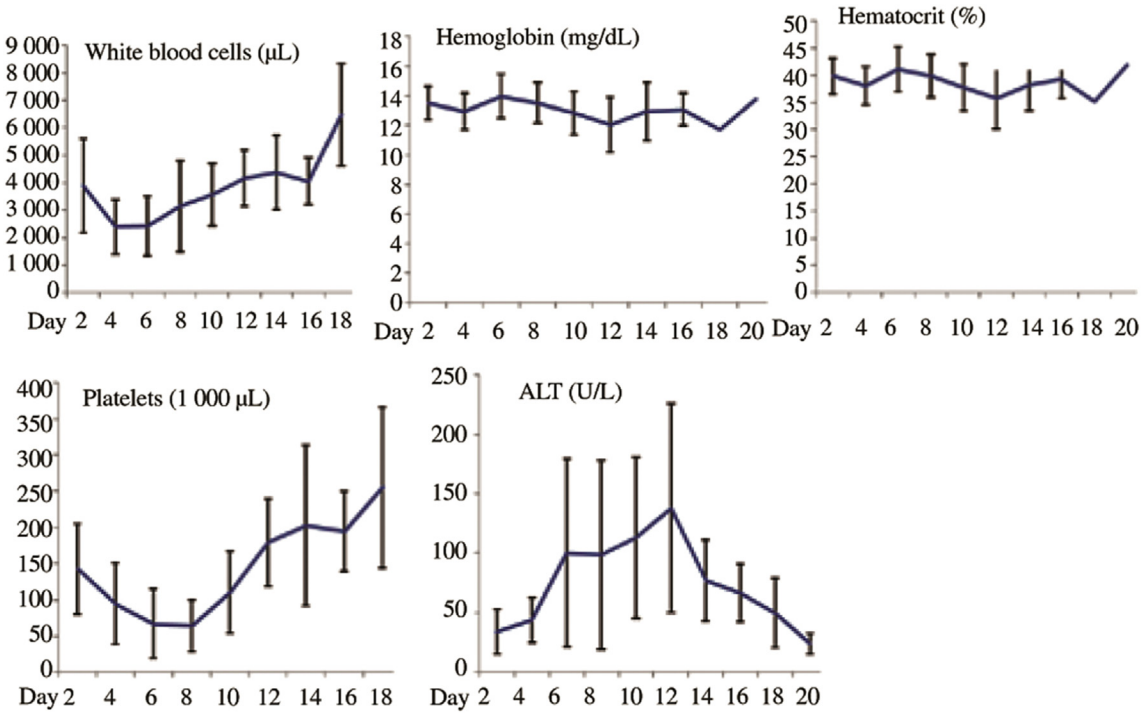

Figure 2. Time-course laboratory data (mean ± SD) obtained from 45 patients with DENV infection.

3.3. Time-course of laboratory data of patients with DENV infections

Figure 2 shows the time-course of laboratory data (mean ± SD) obtained from the 45 patients with DENV infection. We defined the date of fever onset as the first day the disease was detected. The mean leukocyte count and mean platelet count reached their nadirs first on the fourth to eighth day of the illness, followed by the mean alanine aminotransferase (ALT) level, which peaked on the twelfth day, as the mean hemoglobin (Hb)-hematocrit (Hct) level reached the nadir. The mean leukocyte and platelet counts returned to normal levels within 12 d, whereas it took 3 weeks for the mean ALT level to return to normal values.

3.4. Low Hb and Hct dynamic levels in the SN group

Figure 3 shows the time-course laboratory differences between the SP group and the SN group. The average Hb level in the SN group was statistically lower than in the SP group

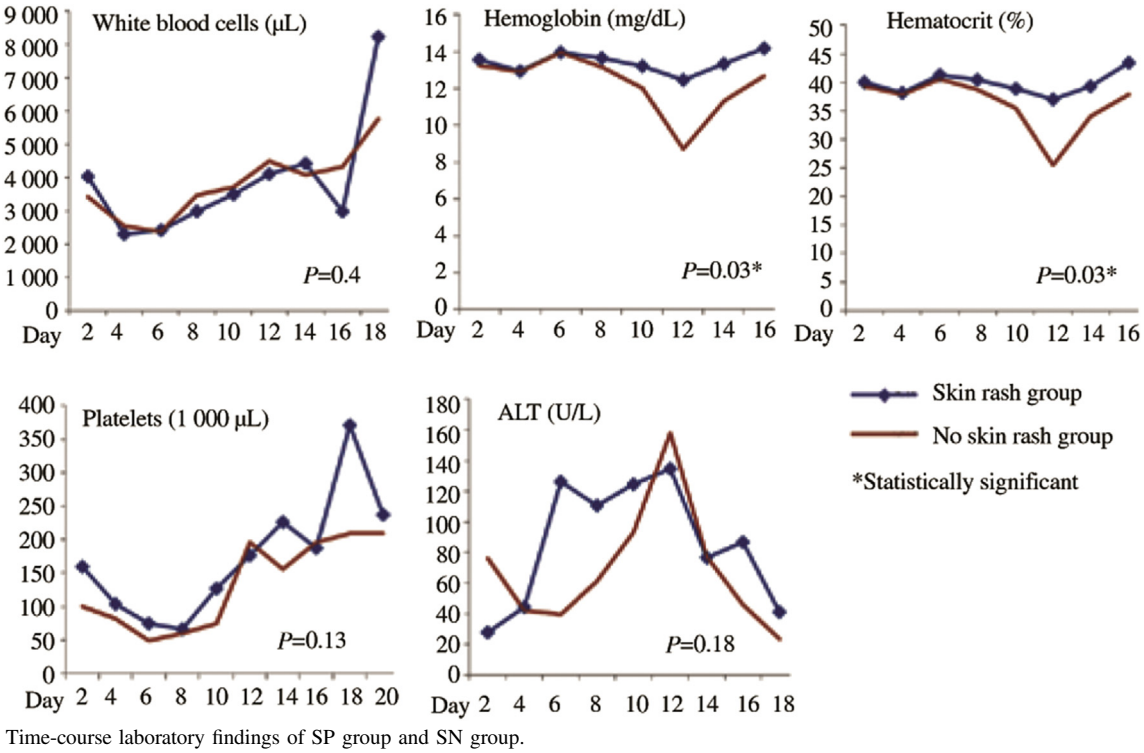

Figure 3. Time-course laboratory findings of SP group and SN group.

(8.7 mg/dL *vs* 12.4 mg/dL, respectively; $P = 0.030$). The average Hct level in the SN group was statistically lower than that in the SP group (25.5% vs 37.05%, respectively; $P = 0.030$). In addition, the SN group had lower mean platelet counts (60 500/μL) compared with the SP group (66 000/μL), even though there was no significant difference statistically ($P = 0.130$). The mean leukocyte and platelet counts reached normal values earlier in the SN group patients than in the SP group.

4. Discussion

This is the first study to investigate the clinical significance of skin rash in DF patients. The pruritic sensation with swollen palms and soles were more common in the SP group than in the SN group. It is interesting to note that more hemorrhagic manifestations, especially genital mucosal involvement, and higher incidence of platelet transfusion, were found in the SN group. Although the SN group was older, we found that platelet transfusion rate had significant correlation with skin rash rather than age. The percentage of dengue hemorrhagic fever in the 4 groups did not differ significantly. Patients with morbilliform rash had a higher incidence of palm/sole swelling and a lower platelet transfusion rate than did patients with the other types of rash. In addition, we found that the mean leukocyte count and mean platelet count reached their nadirs on the fourth to eighth day of the illness, while the mean Hb and Hct levels took about 2 weeks to reach their lowest levels. It took 2–3 weeks for the abnormal laboratory data to be normal. After analyzing the time-course laboratory data, we found that the SN group had lower Hb and Hct levels than did the SP group.

Wu *et al.* reported that skin dendritic cells are likely the initial target of DENV infection in arthropod-borne transmission of virus to humans [9]. These authors demonstrated a novel model for the initial events in arboviral infection. They theorized that damaged small blood vessels give rise to the skin rash noted in DF patients, but there was debate over whether the vessel damage was due to a direct destructive effect of the virus or to another cause [10]. The pathogenesis of skin rash was thought to be caused by the interaction between the virus and host cells, which subsequently led to release of different type of chemical mediators and initiation of the immunological mechanisms [11].

The characteristic exanthem of DF is estimated to occur in 50–82% of patients [9,12]. The initial rash involves a flushing erythema of the face, neck, and chest that typically occurs within the first 24–48 h of the onset of symptoms and is thought to be the result of capillary dilatation. The subsequent rash, seen 3–5 d later, is characterized by a generalized morbilliform eruption with petechiae and islands of sparing ('white islands in a sea of red'), and is thought to be an immune response to the virus [9,13]. Some patients display only the initial rash and recover completely; others develop the more generalized eruption. In our study, 70% of patients showed skin rash, the morbilliform rash was the predominant type.

It is estimated that mucosal involvement occurs in 15%–30% of patients with DENV [11]. Azfai *et al.* [6] and Mahboob *et al.* [13] reported that the oral mucosa is the most common target, while Thomas *et al.* [12] revealed that conjunctival congestion is usually the first symptom of the disease. In our study, only 1 patient had conjunctival involvement, while 4 patients had oral mucosal involvement. However, almost half of our patients presented with genital mucosal involvement, such as hematuria and vaginal bleeding.

In previous studies, only dermatologic manifestations in DENV-infected patients were reported. Besides, the skin rash was often asymptomatic [9]. Edema of the ankle, leg, and face has also been reported in other studies [13]. In our experience, pruritus may be the most uncomfortable symptom, and in this study swollen palms/soles were often noted. However, this is also the first study to evaluate the difference between clinical presentations and disease outcome in patients with or without skin rash.

We also obtained time-course laboratory data for all 45 patients with DENV infections. Itoda *et al.* [14] reported that the mean leukocyte count and mean platelet count reached the nadir on the sixth and eighth days of illness, respectively, and then returned to normal levels within 10 days. We noted a similar pattern in our patients. In addition, mean Hct, Hb, and ALT levels slowly returned to normal within 3 weeks after the disease onset. Chen *et al.* [15] reported that thrombocytopenia may be a useful indicator of severity of dengue infection. In our study, patients in the SN group had more severe thrombocytopenia than did patients in the SP group, even though the difference was not statistically significant ($P = 0.130$). These clinicians should pay more attention to platelet counts in DF patients who do not have a skin rash.

Our results also showed that among DENV patients, morbilliform macules may lead to skin pruritus and swelling of palms or soles, and the disease course and complications were not worse than in patients without skin rash. For patients with skin rash, the pathologic reports revealed superficial perivascular edema, mononuclear infiltration, and endothelial swelling of small blood vessels [16,17]. In a study in Thailand, de Andino *et al.* reported that only 6 of 53 patients with DHF had dengue virus antigen, IgM, and complements in the upper dermal plexus shown by immunofluorescence [16]. Thus, the skin rash may represent a reaction of vessels to cytokines rather than to widespread viral infection. We hypothesized that the skin rash in such patients may be the expression of inflammatory cell infiltration and dermal edema after increased permeability of vessels. The presence of a skin rash suggests the susceptibility of vessels to the cytokines that were produced by an intact immune system. Except for increased itching scores and swelling of palms or soles, there was neither a prolonged disease course nor poor prognosis in the DF patients with skin rash.

Our study had several limitations. First, the number of cases was small. Second, all the cases were collected from the emergency department of our hospital. These patients had relatively more severe and complicated viral infections than would be seen in local clinics. Third, we only followed our patients for about 3 weeks. The long-term outcome between SP and SN groups should be further investigated.

Dengue fever poses a huge burden to any healthcare system. It has a wide clinical spectrum ranging from self-limiting disease to severe fatal illness. The presence of skin rash aids in early diagnosis of dengue fever. Although patients with dengue fever and skin rash have itching and swollen palms and soles, the disease course and complications are not worse than among patients who do not have skin rash.

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