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CLINICAL CHARACTERISTICS AND RISK FACTORS FOR CONCURRENT BACTEREMIA IN ADULTS WITH DENGUE HEMORRHAGIC FEVER

ING-KIT LEE, JIEN-WEI LIU, AND KUENDER D. YANG

Division of Infectious Diseases, Department of Internal Medicine, and Department of Pediatrics, Chang Gung Memorial Hospital-Kaohsiung Medical Center, Taiwan, Republic of China

Abstract. To better understand the clinical characteristics of concurrent bacteremia (dual infection) in patients with dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS) and identify predictive risk factors for dual infection, 100 patients with DHF/DSS (7 with a dual infection and 93 with DHF/DSS alone [controls]) were enrolled in this study. A patient with DHF/DSS who lacked three or more of the five most frequently observed manifestations other than fever in controls or showed disturbed consciousness was defined as one with unusual dengue manifestations. Patients with a dual infection were older, and tended to have prolonged fever, higher frequencies of acute renal failure, gastrointestinal bleeding, altered consciousness, unusual dengue manifestations, and DSS. Acute renal failure (odds ratio [OR] = 51.45, $P = 0.002$), and prolonged fever (> 5 days) (OR = 26.07, $P = 0.017$) were independent risk factors for dual infection. Clinicians should be alert to the potential for concurrent bacteremia when treating patients with DHF/DSS who are at risk for dual infection and manage them accordingly.

INTRODUCTION

A dengue epidemic is one of the most important public health problems in the tropical and subtropical areas.[1–3] Dengue fever (DF) may result from infection with any of the four antigenically related dengue virus serotypes (DEN-1, -2, -3, or -4). The clinical manifestations of DF range from a mild, flu-like and self-limited febrile illness to severe illness with hemorrhagia. Dengue hemorrhagic fever (DHF) in general and its most severe clinical form, dengue shock syndrome (DSS), in particular have been one of the major causes of death among children in some Asian countries where DF is endemic.[4–6]

In Taiwan, dengue epidemics have occurred for many decades.[7] Among the recent dengue epidemics on this island, one outbreak was reported between 1987 and 1988 in southern Taiwan, and a small number of clustered cases of DF have been reported from this area ever since. A large dengue epidemic caused by DEN-2 virus occurred between June and December 2002 in the same regions where a dengue outbreak caused by DEN-1 virus had occurred in 1987–1988.[8,9] There were more than 5,000 cases of symptomatic dengue infection during this outbreak, and seven patients with concurrent DHF and bacteremia were observed at Chang Gung Memorial Hospital-Kaohsiung, a 2,500-bed primary care and tertiary referral medical center in southern Taiwan. Failure in making a diagnosis of concurrent bacteremia infection in patients with DHF may lead to otherwise preventable morbidity and mortality. However, little is known about the risk factor(s) for acquisition of this dual infection.

The aim of the present study was to evaluate the clinical characteristics of patients with concurrent DHF/DSS and bacteremia and to identify risk factors for acquisition of such a dual infection. The identification of such risk factors may help clinicians start timely additional antibiotic therapy in patients with DHF/DSS.

MATERIALS AND METHODS

The study was reviewed and approved by the Institutional Review Board of Chang Gung Memorial Hospital-Kaohsiung. Among 774 patients with the diagnosis of DF admitted to Chang Gung Memorial Hospital-Kaohsiung between June 1, 2002 and December 31, 2002, 127 were found to have DHF/DSS. The diagnosis of DF was made based on either a positive reverse transcriptase–polymerase chain reaction result, a positive enzyme-linked immunosorbent (ELISA) assay result for specific IgM antibody to dengue virus in acute phase serum, or a four-fold increase in dengue-specific hemagglutination inhibition titers in convalescent serum, as previously described.[10,11] The assay for IgM to dengue virus was performed using IgG/IgM capture ELISA kits (Panbio, Windsor, Queensland, Australia). In the dengue capture ELISA, IgM and IgG were determined in separate wells of the assay plate using a common assay method. The values for the DEN IgM capture were calculated by dividing the sample absorbance by the cut-off value (average absorbance of triplicate values of the cut-off calibrator) and multiplying by 10, and a unit > 11 indicated, as per the manufacturer's recommendations, a positive DEN IgM result.[11] The quality assurance of diagnostic tests was confirmed by the Center for Disease Control (Taipei, Taiwan). A diagnosis of DHF was made in patients with laboratory confirmed DF in accordance with the World Health Organization definitions (i.e., presence of fever, hemorrhagia, thrombocytopenia, and overt evidence plasma leakage resulting from increased vascular permeability), and the severity of DHF were further categorized as follows:[12] Grade I = fever accompanied by non-specific constitutional symptoms with the only hemorrhagic manifestation being a positive tourniquet test result; grade II = spontaneous bleeding is observed, in addition to the manifestations of grade I; grade III = circulatory failure manifested by rapid and weak pulse, narrowing of pulse pressure or hypotension, with the presence of cold clammy skin; and grade IV = profound shock with undetectable blood pressure and pulse. Grades III and IV were categorized as DSS.

Patients with a dual infection were those with both DHF/DSS and concurrent bacteremia. Concurrent bacteremia was defined as a positive bacterial culture of blood sampled from a patient less than 72 hours after he or she was hospitalized for DHF/DSS. We excluded patients with nosocomially acquired bacteremia (positive bacterial culture of blood sampled > 72 hours since admission) and those with indeterminate bacteremia, which was characterized as having only one of two sets of blood cultures positive for skin flora.

To determine the clinical characteristics of and risk factors for dual infection, patients with only DHF/DSS were grouped as controls. The controls received only supportive care, including platelet transfusions. Patients who had been treated with an empirical antibiotic before visiting Chang Gung Memorial Hospital-Kaohsiung were excluded. Demographic characteristics, clinical manifestations, and laboratory data (peripheral white blood cell [WBC] count, platelet count, prothrombin time [PT], activated partial thromboplastin time [APTT], and alanine aminotransferase [ALT] level) at admission, serial hematocrit, and serum creatinine level, and clinical course and outcomes of patients with DHF/DSS alone and those with a dual infection were obtained from patient medical records for analyses. Information regarding microorganisms growing in blood culture and the time of initiation of antibiotic therapy was also obtained from patients with a dual infection.

Fever (temperature > 38°C) was found in all patients with DF, regardless of whether they had only DHF/DSS alone or a dual infection. A patient with DHF/DSS who lacked three or more of the five most frequently seen clinical manifestations other than fever in controls, or who had disturbed consciousness was defined as having unusual dengue manifestations. These unusual dengue manifestations were found in approximately 5% of the patients with only DHF/DSS. Acute renal failure was defined as an abrupt decrease in renal function within three days after admission to the hospital. Impaired liver function was defined as a sudden increase in the serum ALT level up to two-fold or more higher than the normal value (normal value < 40 U/L). Prolongation of the PT was defined as > 3 seconds than that of the control, and prolongation of APTT was defined as > 20% than that of the control. Leukocytosis was defined as a peripheral WBC count $> 12.0 \times 10^9$ cells/L, leukopenia as a peripheral WBC count $< 3.0 \times 10^9$ cells/L, and thrombocytopenia as a peripheral platelet count $< 100 \times 10^9$ cells/L.

Statistical analyses. The Mann-Whitney U test was used for comparison of continuous variables, and Fisher's exact test was used for comparison of dichromatic variables of patients with a dual infection and those with DHF/DSS alone. Variables found to be statistically significant in univariate analyses were entered into multivariate analysis using a logistic regression model to identify the independent risk factors for acquisition of a dual infection. A two tailed P value < 0.05 was considered statistically significant.

RESULTS

Among 127 patients with DHF/DSS, 7 (5.5%) with concurrent bacteremia were classified as having a dual infection, 93 as controls, and 27 patients were excluded because of either indeterminate significance of their skin flora bacteremia or the use of an antibiotic for presumptive sepsis before visiting Chang Gung Memorial Hospital-Kaohsiung. With regard to concurrent bacteremia, *Klebsiella pneumoniae* was isolated from three patients, and *Rosemonas* species, *Moraxella lacunata*, *Klebsiella ozaenae*, and *Enterococcus faecalis* were isolated from one patient each. The demographic characteristics, clinical manifestations, and laboratory data of enrolled patients with DHF are summarized in Tables 1, 2, and 3, respectively.

TABLE 1
Characteristics of patients with dual infection and those with DHF/DSS alone (controls)*

Variable	Dual infection group (n = 7)	Control group (n = 93)	P
Sex (M/F ratio)	4/3	50/43	1.000
Median age, years (range)	70.0 (47–75)	52.0 (22–88)	0.007
Underlying disease			
Hypertension (%)	4 (57.1)	22 (23.6)	0.073
Diabetes mellitus (%)	2 (28.5)	6 (6.4)	0.096
Malignancy (%)	1 (14.2)	2 (2.1)	0.197
Adrenal insufficiency (%)	1 (14.2)	3 (3.2)	0.255
Duration of fever, days, median (range)	8.0 (2–14)	4.0 (2–9)	0.004
DSS (%)	3 (42.8)	3 (3.2)	0.004

* DHF/DSS = dengue hemorrhagic fever/dengue shock syndrome.

Of the seven patients (four men and three women; median age = 70 years, [range = 47–75 years]; median duration of fever = 8 days [range = 2–14 days]) with dual infection, four had grade II DHF and three had grade III DHF. Apart from fever, the three most common clinical manifestations other than fever in patients with a dual infection were petechiae, bone pain, and gum bleeding, each accounting for 71.4% (Table 2). Three (42.8%) of seven patients with dual infection (two with grade II DHF and one with grade III DHF) experienced unusual dengue manifestations (Table 2). Of these three patients, two (28.5% of the dual infections) had altered consciousness that was fatal (one with *K. pneumoniae* meningitis and the other with active gastrointestinal bleeding and *E. faecalis* bacteremia); the third patient was admitted with fever and swelling of his cheek, and his blood culture was positive for *K. ozaenae*. The details of the seven patients with dual infections are summarized in Table 4.

Of the 93 controls (50 men and 43 women, median age = 52 years [range = 22–88 years]; median duration of fever = 4 days [range = 2–9 days]), 5 had grade I DHF, 85 had grade

TABLE 2
Signs/symptoms and mortality rate in patients with dual infection and those with DHF/DSS alone (controls)*

Symptom/sign	Controls n = 93 (%)	Dual infection n = 7 (%)	P
Fever	93 (100)	7 (100)	–
Petechiae	73 (78.4)	5 (71.4)	0.647
Bone pain	67 (72)	5 (71.4)	1.0
Abdominal pain	64 (68.8)	4 (57.1)	0.677
Myalgia	60 (64.5)	4 (57.1)	0.700
Headache	57 (61.2)	3 (42.8)	0.433
Gum bleeding	32 (34.4)	5 (71.4)	0.098
Nausea	26 (27.9)	3 (42.8)	0.410
Skin rash	22 (23.6)	2 (28.5)	0.672
Cough	20 (21.5)	3 (42.8)	0.197
Gastrointestinal bleeding	19 (20.4)	4 (57.1)	0.047
Retro-orbital pain	13 (13.9)	3 (42.8)	0.079
Hemoptysis	4 (4.3)	1 (14.2)	0.310
Diarrhea	3 (3.2)	1 (14.2)	0.255
Altered consciousness	1 (1.1)	1 (14.2)	0.012
Facial swelling	0 (0)	1 (14.2)	0.070
Unusual dengue manifestations†	5 (5.3)	3 (42.8)	0.010
Mortality	1 (1.1)	2 (28.5)	0.012

* An individual patient might have more than one symptom and/or sign. DHF/DSS = dengue hemorrhagic fever/dengue shock syndrome.
† Unusual dengue manifestations were defined as absence of ≥ 3 of the 5 leading manifestations other than fever (e.g., petechiae, bone pain, abdominal pain, myalgia, and headache) found in 93 controls and/or presence of altered consciousness.

TABLE 3
Laboratory findings in patients with dual infection and those with DHF/DSS alone (controls)*

Variable	Dual infection A/B (%)	Controls A/B (%)	*P*
Leukocytosis (WBCs > 12.0×10^9 cells/L)	1/7 (14.2)	4/93 (4.3)	0.310
Leukopenia (WBCs < 3.0×10^9 cells/L)	3/7 (42.8)	67/93 (72)	0.193
Thrombocytopenia (< 100×10^9 cells/L)	7/7 (100)	93/93 (100)	–
Prolongation of APTT†	5/5 (100)	68/69 (98.5)	1.0
Prolongation of PT‡	0/5 (0)	3/65 (4.6)	1.0
Elevated ALT (> 40 U/L)	6/7 (85.7)	66/76 (86.8)	1.0
(range)	(90–1,651)	(43–1,030)	
Acute renal failure	5/7 (71.4)	4/81 (4.9)	< 0.001
Peak of hematocrit (%)§			0.124
Mean ± SD	37.2 ± 8.57	40.5 ± 4.68	
Median (range)	36.6 (28.2–53.2)	40.1 (30.5–50.7)	

* DHF/DSS = dengue hemorrhagic fever/dengue shock syndrome; A = No. of patients; B = No. of patients with data available; WBCs = white blood cells; APTT = activated partial thromboplastin time; PT = prothrombin time; ALT = alanine aminotransferase.
† Prolongation of the APTT was defined as > 20% of the control.
‡ Prolongation of the PT was defined as > 3 seconds than the control.
§ All patients in both groups had data available.

II DHF, 2 had grade III DHF, and 1 had grade IV DHF. The five most common clinical manifestations other than fever in these 93 controls were petechiae (78.4%), bone pain (72%), abdominal pain (68.8%), myalgia (64.5%), and headache (61.2%) (Table 2). Five (four with Grade II DHF and one with grade III DHF) of the 93 controls (5.3%) showed unusual dengue manifestations. Among them, four had active gastrointestinal bleeding and one had abdominal pain and acute cholecystitis. Of the 93 controls, only one with grade IV DHF died.

The differences in peripheral leukocytosis, leukopenia, thrombocytopenia, peak hematocrit, PT and APTT prolongations, and elevated serum ALT levels were not significantly between patients with dual infection and those with DHF/DSS alone (Table 3). However, five (two with grade II DHF and three with grade III DHF) of seven patients (71.4%) with a dual infection had acute renal failure. Four (two with grade II DHF, one with grade III DHF, and one with grade IV DHF) of 81 controls (4.9%) with available data had acute renal shutdown ($P < 0.001$). Of note, the four controls with acute renal failure all had active gastrointestinal bleeding.

Univariate analyses showed that in a comparison of patients with dual infection and those with only DHF/DSS, differences in mortality rate (28.5% versus 1.1%; $P = 0.012$), age (median = 70 versus 52 years; $P = 0.007$), prolonged fever (median duration of fever = 8 versus 4 days; $P = 0.004$), acute renal failure (71.4% versus 4.9%; $P < 0.001$), gastrointestinal bleeding (57.1% versus 20.4%; $P = 0.047$), altered consciousness (14.2% versus 1.1%; $P = 0.012$), unusual dengue manifestations (42.8% versus 5.3%; $P = 0.010$), and DSS (42.8% versus 3.2%; $P = 0.004$) were statistically significant. Multivariate analysis showed that acute renal failure (odds ratio [OR] = 51.45, 95% confidence interval [CI] = 4.35–607.58, $P = 0.002$) and prolonged fever (> 5 days) (OR = 26.07, 95% CI = 1.78–381.53, $P = 0.017$) were independent predictive factors for concurrent bacteremia in patients with DHF/DSS.

DISCUSSION

This series indicated that 5.5% of the patients with DHF/DSS also had concurrent bacteremia. It is uncertain whether this incidence of dual infection assessed at a medical center reflects that in general population. As the patients were admitted to a tertiary center, our study population was probably biased by patient selection and referral pattern. Dual infection was seldom discussed in the past, and has been sporadically published in case reports.[13–16] This has hindered a widespread awareness of concurrent bacteremia in patients with DHF/DSS. As a result, clinicians are inevitably less aware of the potential for dual infection when treating patients with DHF/DSS who are at high risk for concurrent bacteremia.

Unlike the predominant pediatric patients with DHF/DSS seen in southeast Asia,[4–6] all the patients with DHF/DSS in the present study were either young adults or elderly individuals. To our knowledge, this is the one of few detailed reports of DHF in the elderly.[4,5,8,17,18] An elderly (≥ 50 years old) age was previously reported to be a risk factor for mortality in patients with DF.[17,18] In general, the aging-adherent co-morbidities and waning immunity pose a substantial risk for fatality in elderly patients with active infection.[19,20] For the same reason, elderly individuals with a dengue virus infection are more likely to develop a critical condition, and were at risk for acquisition of bacterial coinfections, but not for concurrent bacteremia, as was specifically addressed in this study.

The clinical manifestations of 93 control patients were similar to those in other reported series.[4,5,12] The infrequently encountered neurologic manifestations of DF, such as altered consciousness, convulsions, and coma, have been increasingly reported in recent years.[21–24] In an attempt to enhance the clinical diagnosis of a dual infection, purposefully designed unusual dengue manifestations, defined as a patient with DHF/DSS who lacked three or more of the five leading dengue manifestations observed in controls and/or who had disturbed consciousness, was used as a potential risk factor in the analysis in this study. Although unusual dengue manifestations were not an independent predictive factor for concurrent bacteremia in the present report, these deserve further study in other populations to determine whether unusual dengue manifestations are an applicable predictive factor for acquisition of concurrent bacteremia in patients with DHF/DSS because patients with a dual infection in this series were older (median age = 70 years for the dual infection group versus 52 years for the control group), and elderly patients infected with dengue virus might have atypical clinical presentations.

TABLE 4
Details of seven patients with DHF/DSS and concurrent bacteremia*

Patient no.	Age (years), sex	Underlying disease	Initial laboratory data	Severity of DHF	Day of blood sampled for culture†	Clinical clue suggesting bacterial infection	Isolated bacterium	Bacterial infection source	Antibiotic treatment‡	Outcome
1	47, F	Uterus myoma	WBCs = 4.4×10^9/L PLT = 7.0×10^9/L PT = 10.8 sec APTT = 47.8 sec ALT = 30 U/L Hct = 36.6%	Grade II	Day 3	Prolonged fever (8 days)	*Rosemonas* species	Primary bacteremia	PIP plus GM, switched to AMC	Survived
2	70, M	Hypertension	WBCs = 2.8×10^9/L PLT = 3.0×10^9/L PT = 11.4 sec APTT = 47.8 sec Hct = 28.8% ALT = 1,651 U/L Cr = 2.1 mg/dL	Grade II	Day 2	Drowsiness	*Klebisella pneumoniae*	Bacterial meningitis	PIP plus AN, switched to CRO	Died
3	75, F	Hypertension, cervical cancer	WBCs = 8.7×10^9/L PLT = 43×10^9/L Hct = 39.9% ALT = 91 U/L	Grade II	Day 2	Prolonged fever (11 days)	*Klebsiella pneumoniae*	Primary bacteremia	CF plus GM	Survived
4	55, M	Alcoholism	WBC = 2.9×10^9/L PLT = 2.0×10^9/L Hct = 53.2% PT = 11.7 sec APTT = 73.4 sec ALT = 1,596 U/L Cr, 4.6 mg/dL	Grade III	Day 3	Prolonged fever (14 days)	*Klebsiella pneumoniae*	Primary bacteremia	CF plus GM	Survived
5	68, F	Diabetes mellitus, hypertension, adrenal insufficiency	WBCs = 10×10^9/L PLT = 13×10^9/L Hct = 33.5% PT = 10.4 sec APTT = 46.1 sec ALT = 134 U/L Cr = 2.2 mg/dL	Grade III	Day 2	Prolonged fever (10 days)	*Moraxella lacunata*	Primary bacteremia	CF plus GM, switched to Oxa	Survived
6	70, M	Diabetes mellitus, hypertension	WBCs = 2.5×10^9/L PLT = 9.0×10^9/L Hct = 40.7% PT = 11.8 sec APTT = 38.4 sec Cr = 2.9 mg/dL Glu = 788 mg/dL ALT = 90 U/L	Grade II	Day 1	Cheek swelling	*Klebisella ozaenae*	Facial cellulitis	CC plus GM, switched to CF	Survived
7	70, M	Parkinsonism	WBCs = 23×10^9/L PLT = 14×10^9/L Hct = 28.2% Cr = 2.3 mg/dL ALT = 154 U/L	Grade III	Day 1	Leukocytosis, drowsiness	*Enterococcus faecalis*	Primary bacteremia	PEN plus CRO	Died

* DHF = dengue hemorrhagic fever; DSS = dengue shock syndrome; WBCs = white blood cells; PLT = platelets; PT = prothrombin time; APTT = activated partial thromboplastin time; ALT = alanine aminotransferase; Hct = hematocrit; Cr = creatinine; Glu = glucose.

† Except for patient 4 whose antibiotics were prescribed on day 5, all patients received antibiotic therapy after blood was drawn for culture.

‡ PIP = piperacillin; GM = gentamicin; AMC = amoxicillin/clavulanate; AN = amikacin; CRO = ceftriaxone; CF = cefazolin; Oxa = oxacillin; CC = clindamycin; PEN = penicillin.

Prolonged fever and acute renal failure were independent predictive factors for dual infection in this study. Generally, DHF/DSS begins with a sudden increase in body temperature, and dengue viruses always disappear from the blood of the host an average of five days later, which is closely correlated with the disappearance of fever.[4,25] Our study also suggests that patients with DHF/DSS who also have prolonged fever (> 5 days) are at high risk for concurrent bacteremia. Acute renal failure, a rarely encountered manifestation in patients with DHF,[26] may result from excessive plasma leakage, massive active hemorrhage, or DSS.[26,27]

Rhabdomyolysis, an unusual complication in DF, may cause multiorgan failure in patients with DHF.[28,29] Hemolysis and, perhaps, rhabdomyolysis particularly tend to develop in patients with an underlying glucose-6-phosphate dehydrogenase (G6PD) deficiency once they acquire DF, and these complications will always lead to acute renal failure.[30] Taiwan has a low prevalence of G6PD deficiency of approximately 2.0%,[31] and none of the patients in this series was tested for G6PD deficiency. With regard to the five cases of acute renal failure in our study, it is unclear whether the sudden shutdown of renal function results from the synergistic effect of bacteremia and DSS because shared proinflammatory mediators were found in each of these infection entities.[32]

As for the pathogens isolated from blood in bacteremic patients in this series, with the exception of one isolate of *Rosemonas* species and another isolate of *K. ozaenae*, the majority of the bacteria (three isolates of *K. pneumoniae*, one of *M. lacunata*, and one of *E. faecalis*) are normally found in the intestinal tract. It is reasonable to presume that most of the above mentioned bacteria invaded the bloodstream from the intestinal lumens of the patients because dengue virus infections may lead to disintegration of intestinal mucosal barrier, resulting in creation of a portal of entry for pathogens that normally inhabit the intestinal tract.[33,34]

There are some limitations in the present study. First, the small number of study cases with a dual infection makes statistical power quite small for multivariate analysis for predictive factors for concurrent bacteremia in patients with DHF/DSS. Second, it was conducted at a single medical center, and the patient population and clinical characteristics may be biased by referral pattern. Third, this study of exclusively adult patients makes it uncertain if the identified risk factors for concurrent bacteremia in DHF/DSS are applicable to pediatric patients. Further studies to elucidate more information regarding clinical characteristics of dual infection are warranted. Because of the possible overlapping clinical manifestations of both infections, concurrent bacteremia is easily overlooked in a dengue endemic setting. Failure to make a timely diagnosis of dual infection and starting early additional antibiotic therapy accordingly will put the affected patients in jeopardy. In conclusion, to avoid otherwise preventable mortality and morbidity, clinicians should be alert to the potential for a concurrent bacteremia when facing a patient with DHF/DSS with a prolonged fever (>5 days) and/or acute renal failure, and therefore initiate a timely additional antimicrobial treatment until blood cultures are negative.

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Authors' addresses: Ing-Kit Lee and Jien-Wei Liu, Division of Infectious Diseases, Department of Internal Medicine, Chang Gung Memorial Hospital-Kaohsiung Medical Center, Taiwan, Republic of China. Fax: 866-7-73220402, E-mail: 88b0@adm.cgmh.org.tw. Kuender D. Yang, Department of Pediatrics, Chang Gung Memorial Hospital-Kaohsiung, Taiwan, Republic of China.

Reprint requents: Dr. Jien-Wei Liu, Division of Infectious Diseases, Department of Internal Medicine, Chang Gung Memorial Hospital-Kaohsiung Medical Center, No. 123, Ta Pei Road, Niao Sung Hsiang, Kaohsuing Hsien, Taiwan 833, Republic of China.

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