

Pediatric acute febrile mucocutaneous lymph node syndrome with characteristic desquamation of fingers and toes: my clinical observation of fifty cases*

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1. INTRODUCTION

Since “herpes iris conjunctivae” was first reported by Fuchs in 1876,¹ many disease names have been given to syndromes that involve eyes, skin and mucous membranes. All these syndromes were combined together as mucocutaneous-ocular syndrome by researchers such as Franceschetti and Valerio in 1939–1940^{2,3} and Proppe in 1948⁴ and become considered as a subtype of erythema exudativum multiforme. In Japan a study group of the Japanese Ministry of Education in 1958 recategorized this syndrome and divided it into three groups: (1) erythema exudativum multiforme syndrome; (2) Behçet’s syndrome; and (3) Reiter’s disease.^{4,5} However, I have experienced a syndrome that does not fit any of these categories. I have observed 50 cases similar to so-called mucocutaneous-ocular syndrome, but different in various points, during approximately 6 years from January 1961 to November 1966.

The following is a list of its characteristics: (1) even with the use of various antibiotics, fever higher than 38°C persists longer than 6 days; fever lasting ~1 to 2 weeks: 50 cases (100%); (2) bilateral bulbar conjunctival injection: 49 cases (98%); (3) erythematous rash can be seen particularly on both palms and/or soles, but never forms vesicles: 43 cases (86%); (4) redness, dryness, erosion and cracking of the lips, sometimes with bleeding and hemorrhagic scabbing, and sometimes diffuse injection of the oral mucosa and strawberry tongue are recognized: 48 cases (96%); formation of

vesicles, ulcers, pseudomembranes or aphthae are never seen; (5) acute swelling of neck lymph nodes (equal to or bigger than the head of the thumb) is seen but never suppurates: 33 cases (68%); (6) both hands and feet exhibit vasoneurogenic edema: 22 cases (44%); (7) desquamation starts from the nail-skin junction of the fingers and toes, mostly beginning in the second week of the disease: 49 cases (98%); (8) more than half of the cases are younger than 2 years: 27 cases (54%); (9) no recurrence; (10) it heals without intervention and without sequelae; (11) no contagion between siblings was observed.

At first I focused on the special desquamation and presented seven cases at the 61st Chiba Prefecture Pediatric Meeting in October 1962,⁶ with a title of “Non-scarlet fever desquamation syndrome,” which means a syndrome somewhat similar to but different from scarlet fever, and associated with desquamation.

As I experienced more cases, judging from the changes in the eyes, skin and mucous membranes, I thought that these cases belonged to the so-called mucocutaneous-ocular syndrome, even though many of the clinical signs were milder than Stevens-Johnson syndrome and “pluriorificielle ectodermose.” So I made my second presentation with a title of “Twenty cases of ocular-mucocutaneous syndrome” at the United Pediatric Convention of Eastern and Central Japan in Matsumoto, Japan, October 1964.⁷

But later, after more precise examination of the conventional reports about so-called mucocutaneous-ocular syndrome (MCOS), I realized that our syndrome is a unique clinical entity, which is not identical with any type of MCOS ever reported. Therefore I present the clinical analysis and laboratory data of 50 cases we experienced as well as a review of the literature, and I hope to hear your opinion.

2. CASE REPORTS

Here I present 7 cases in detail, chosen from 50 cases hospitalized at the Japan Red Cross Central Hospital from January 1961 to the end of November 1966 (Table 1). The case numbers do not correspond with the case numbers described later. Figures 1 to 4 show data

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*Originally received January 19, 1967 and published in the *Japanese Journal of Allergy* 1967;16(3):178–222 [in Japanese]. An English abstract was published with the Japanese text of this article in 1967. The title of the English abstract was, “Febrile oculo-oro-cutaneo-acrodesquamatos syndrome with or without acute non-suppurative cervical lymphadenitis in infancy and childhood: clinical observation of 50 cases.” Tomisaku Kawasaki and Fumio Kousaki were listed as coauthors.

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Table 1. Our 50 cases ordered by age and classified according to main symptoms. Cases #1-33: cervical lymphadenopathy (CLA) (+) group, Cases #34-50: CLA (-) group.

Case #	Age	Sex	Fever	CLA	Skin		Congested bulbar conjunctivae	Oral symptoms	Edematous swelling of hands and feet
					Rash	Peeling			
1	4m	m	+	+	+	+	+	+	-
2	6m	m	+	+	+	+	+	+	-
3	8m	m	+	+	+	+	+	+	+
4	8m	m	+	+	+	+	+	+	+
5	8m	m	+	+	-	+	+	+	-
6	11m	m	+	+	+	+	+	+	+
7	1y	f	+	+	+	+	+	+	+
8	1y2m	m	+	+	+	+	+	+	+
9	1y2m	f	+	+	+	+	+	+	+
10	1y7m	f	+	+	-	+	+	+	+
11	1y8m	m	+	+	+	+	+	+	+
12	1y9m	f	+	+	+	+	+	+	+
13	1y10m	m	+	+	+	-	+	+	+
14	1y11m	m	+	+	+	+	+	+	+
15	2y3m	f	+	+	+	+	+	+	-
16	2y10m	m	+	+	+	+	+	+	+
17	3y2m	f	+	+	+	+	+	+	+
18	3y4m	f	+	+	+	+	+	+	-
19	3y6m	f	+	+	+	+	+	+	-
20	3y7m	m	+	+	+	+	+	+	-
21	3y9m	f	+	+	+	+	+	+	+
22	4y1m	f	+	+	+	+	+	+	+
23	4y2m	f	+	+	+	+	+	+	-
24	4y3m	m	+	+	+	+	+	+	-
25	4y7m	m	+	+	-	+	+	+	-
26	5y1m	m	+	+	+	+	+	+	-
27	5y8m	f	+	+	+	+	+	+	-
28	5y10m	m	+	+	+	+	+	+	-
29	6y4m	f	+	+	+	+	+	+	-
30	6y9m	m	+	+	+	+	+	+	-
31	7y1m	f	+	+	+	+	+	+	-
32	8y7m	m	+	+	+	+	+	+	-
33	9y1m	m	+	+	+	+	+	+	-
34	2m	m	+	-	+	+	+	+	-
35	3m	f	+	-	-	+	+	+	-
36	6m	m	+	-	+	+	+	+	+
37	7m	m	+	-	+	+	-	+	+
38	8m	m	+	-	+	+	+	+	-
39	9m	m	+	-	+	+	+	+	-
40	11m	m	+	-	+	+	+	-	-
41	11m	m	+	-	+	+	+	+	-
42	1y3m	m	+	-	+	+	+	+	+
43	1y5m	m	+	-	+	+	+	+	+
44	1y7m	m	+	-	+	+	+	+	+
45	1y10m	m	+	-	+	+	+	+	-
46	1y11m	m	+	-	+	+	+	+	+
47	2y2m	m	+	-	+	+	+	-	-
48	2y3m	f	+	-	-	+	+	+	-
49	2y7m	m	+	-	-	+	+	+	+
50	3y4m	f	+	-	+	+	+	+	-

recorded at the time of hospitalization, and the color of the eyes, lips and rash is red.

Case 1: male, 4 years 3 months (Case 24). Admitted. January 5, 1961.

Discharged. February 9, 1961.

Family history. Father has an allergic tendency,

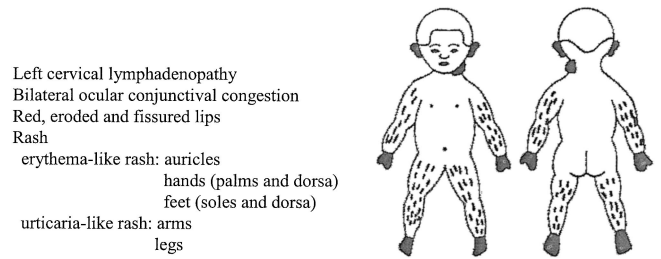


FIG. 1. Case 2 (1 year 8 months).

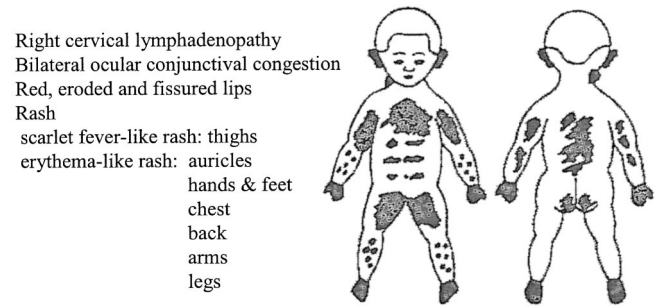


FIG. 2. Case 3 (8 months).

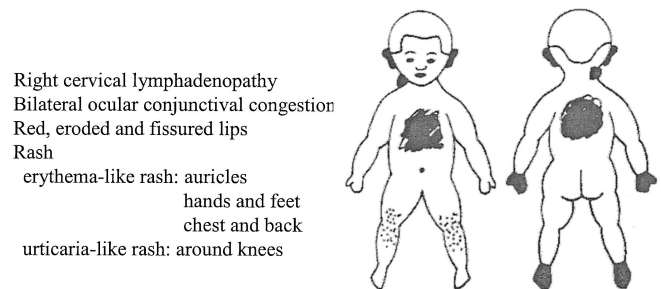


FIG. 3. Case 4.

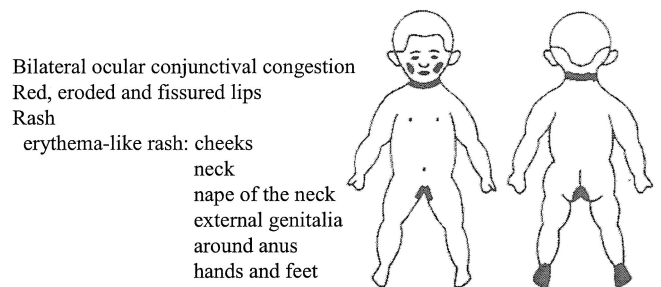


FIG. 4. Case 5 (1 year 2 months).

recurrent eczema from birth and easily develops rashes to drugs. Mother is healthy.

Past history. Normal delivery. Breast feeding. Severe eczema in infancy. Normal growth. A common cold always triggered wheezing.

Present history. On the night of December 30, 1960, the patient complained of neck pain, and swelling of the left neck was recognized.

December 31: Swelling of the left neck became more distinct, and he complained of pain to palpation. Fever began (38.5°C).

January 1, 1961: Fever persisted (38.5–39.0°C), and occasionally he complained of abdominal pain.

January 2: Seen by a doctor and diagnosed with pharyngitis. He vomited medication. Temperature 38.5–39.0°C.

January 3: Patient vomited frequently. He was given chloromycetin (chloramphenicol) 600 mg/day. Temperature 38.5–39.0°C.

January 4: Fever increased to 40°C and he vomited ground-coffee-like substance.

January 5: Admitted to hospital. Status on admission: dehydrated. General condition was poor with tachypnea and tachycardia. Consciousness level was normal. Patient had bilateral bulbar conjunctival injection. Lips were crimson, dry and fissured. The oral mucosa was reddened diffusely, and a strawberry tongue was noted. No pseudomembrane, ulcers or aphthae were observed. Left cervical lymph nodes were diffusely swollen and tender to palpation, but there was no overlying erythema of the skin. Palms and soles were extremely red bilaterally. No other rash was observed. Heart and lungs were normal. The liver edge was palpable and the spleen was not.

Clinical course after admission. See Temperature Chart 1 as a reference.

To correct severe dehydration, patient received intravenous fluids and hostacyclin (tetracycline) (125 mg/day), and intramuscular injections of penicillin (900 000 U [units]/day) were initiated.

January 6: Skin became icteric. Screening of cerebrospinal fluid was normal. Methylprednisolone 10 mg was given intramuscularly.

January 7: Erythematous rash developed over entire body. High fever continued.

January 9: Left cervical lymphadenopathy diminished, but right cervical lymph nodes became enlarged.

January 10: Bilateral injection of the bulbar conjunctive persisted as before. Rash and mild icterus still present. Patient recovered enough to take some food.

January 12: Desquamation started from the nail-skin junction of the right second finger. Rash still present. Liver was palpable two finger breadths below costal margin. Laboratory evaluation of hepatic function showed that the icterus index was 20, total serum bilirubin was 2.6 mg/dl, direct bilirubin was 1.5 mg/dl, indirect bilirubin was 1.1 mg/dl, CCF was weakly positive, TAKATA was negative.

January 13: Fever finally resolved. Desquamation noted on all fingers.

January 14: Injection of bulbar conjunctive diminished. Only icterus persisted. Cervical lymph nodes no longer enlarged. Rash diminished.

January 16: Icterus still present. Severe anemia was recognized. Laboratory data included WBC [white blood cell count] 15 600: 72% neutrophils, 5% band forms, 1% myelocytes, 1% metamyelocytes 12% lymphocytes, 3% monocytes, 1% eosinophils; Hgb [hemoglobin] 8.2 g/dl, RBC [red blood cell count] 2.6×10^6 Hct [hematocrit] 21%; icteric index 26.7, total bilirubin 4.8 mg/dl, direct bilirubin 2.6 mg/dl, indirect bilirubin 2.2 mg/dl, TTT 4.0 microunits, Gros (+), CCF (-), TAKATA (-).

January 18: Membranous desquamation started from the nail-skin junction of toes. Icterus diminished.

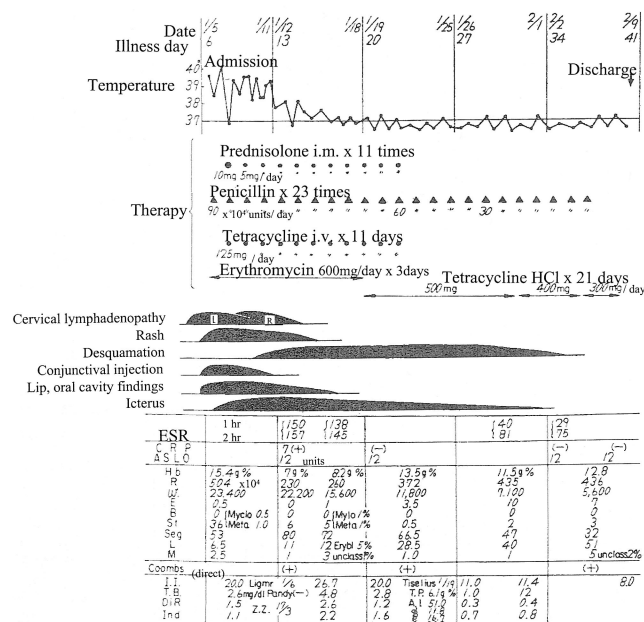
January 24: Patient smiled for the first time. Icterus of skin and bulbar conjunctive barely visible. Only the edge of liver was palpable.

February 1: Laboratory data: serum icterus index 11.4, total bilirubin 1.2 mg/dl, direct bilirubin 0.4 mg/dl, indirect bilirubin 0.8 mg/dl.

February 9: Recovered completely and discharged. Icterus index 8.0.

Treatment. As depicted in the temperature chart, 10 mg/day prednisolone im was given on January 6 and 5 mg/day from January 7 for 10 days. Penicillin 900 000 U/day was given intramuscularly starting January 5 for 11 times, then 600 000 U for 5 times, followed by 300 000 U for 7 times for a total of 23 times. In addition hostacyclin 125 mg/day with hydration and vitamins were administered intravenously for 11 days. Also oral erythromycin 600 mg/day was given for 13 days along with oral acromycin 300 to 500 mg/day for 21 days.

Laboratory data. As shown in the temperature chart, this case presented with anemia and icterus caused by severe hemolytic anemia and a markedly elevated erythrocyte sedimentation rate (ESR) (150 mm/h), which made me think of autohemagglutination. When I set up the ESR tube, I noted that the sedimentation was very rapid, so I performed a direct Coombs test, which was positive.



TEMPERATURE CHART 1.

This was our first case, and in the end we did not make a diagnosis. Since this patient had cervical lymphadenitis and bilateral conjunctival injection, a generalized erythematous rash, especially on the palms and soles, marked injection of the lips and oral mucosa and strawberry tongue, I thought of scarlet fever but rejected that diagnosis because there was no abnormality in the perineal or perianal area and the desquamation, instead of being generalized, occurred only at the nail-skin junction of the fingers and toes. I also considered Stevens-Johnson syndrome or ectodermosis erosiva pluriorificialis but rejected these diagnoses.

Although I only had this one case in 1961, I started to see more cases the next year, and began to pay attention to the uniqueness of this syndrome.

Case 2: male, 1 year 8 month (Case 11). *Admitted.* March 30, 1963.

Discharged. April 13, 1963.

Chief complaint. Lymphadenopathy, fever.

Family history. The father was in good health. The mother had frequent urticaria during pregnancy. She also developed a rash from penicillin.

Past history. Born by cesarean section, weighed 3100 g at birth. He was fed formula. Normal growth. He had mild eczema during infancy. He had wheezing with colds.

Present history. March 23, 1963: The patient had a left cervical lymph node about the size of the head of the little finger. He also had a fever of 39°C.

March 24: The mother noticed that his left lymph node was swelling to about the size of a chicken egg. He had red lips with erosion and fissures. He was given chloromycetin syrup when he had a fever of 38.7°C.

March 25: His primary doctor diagnosed cervical lymphadenitis. White blood cell count was 17 600/mm³.

March 26: The patient developed edematous hands and feet with a fever of >39°C. He also had an erythematous rash.

March 27: When fever reached 39.7°C he was given a blood examination by the primary doctor. The ESR was elevated (106 mm/1 h and 127 mm/2 h). He had bilateral ocular conjunctival injection, obvious erythema of both palms and soles, erythema of both arms and the extensor side of the legs. The primary doctor suspected rheumatic fever. The patient was treated with oral antibiotics: chloromycetin 750 mg/day and penicillin 1 000 000 U/day.

March 28: He had a fever of 38.5°C. Ocular conjunctival injection and erythema increased.

March 29: The primary doctor referred him to us to rule out sepsis.

March 30: He was hospitalized in our department.

Physical examination on admission. He had obvious bilateral conjunctival injection. His lips were dry, red, eroded and fissured. His oral cavity was diffusely red,

but there was no aphthae, ulcers or pseudomembrane. Left cervical lymph nodes were as big as a chicken egg (Photograph 17) and elastic and firm. He had severe pain in the cervical lymph nodes when he was touched or moved. However, there was no erythema overlying the cervical lymphadenopathy. Figure 1 shows the area of the rash. The rash was mainly macular or urticaria-like on the extremities. There was no rash on the body. Both hands and feet were edematous, like angioneurotic edema, and very taut. There were no changes of the external genitalia and anus.

Clinical course in the hospital. See Temperature Chart 2.

March 30: Only a small amount of blood around the needle was obtained by needle puncture of the cervical lymph node. Culture of this blood for bacteria yielded no organisms.

April 1: The rash began to disappear.

April 2: Bilateral ocular conjunctival injection was almost resolved.

April 3: The rash had almost disappeared leaving a slight residual pigmentation. Desquamation of fingers started from between the nail and the exposed skin at the tip of the finger.

April 4: The edema of both hands and feet disappeared completely.

April 6: Desquamation of right first toe started from between the nail and the exposed skin at the tip of the toe.

April 8: Cervical lymphadenopathy disappeared completely. The lip erosion and fissuring resolved.

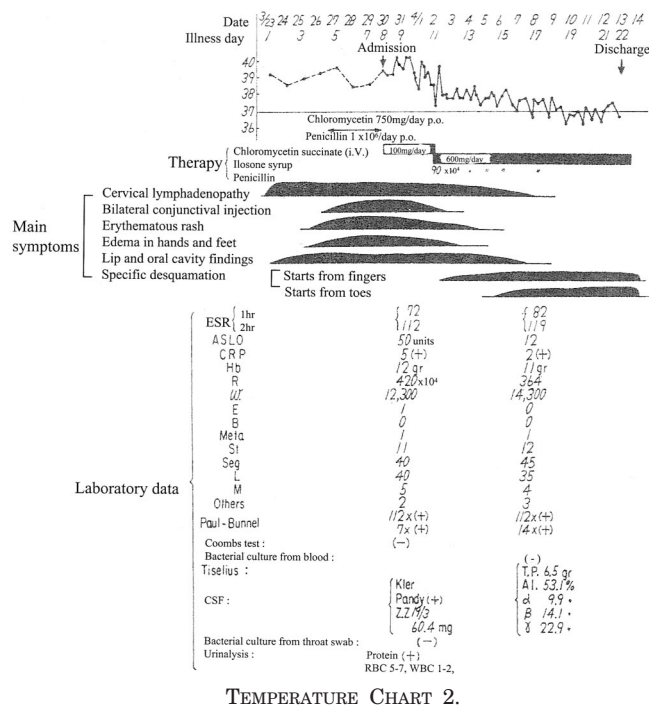
April 13: He still had bilateral desquamation of the hands and feet. However, he had completely recovered and was discharged.

Laboratory data. See Temperature Chart 2.

April 2: ESR 72 mm/1 h, 112 mm/2 h, CRP [C-reactive protein] 5 (+), ASLO [anti-streptolysin O] 50 U,



PHOTOGRAPH 17. Case 11. Swelling of a lymph node at the left side of the neck; drying, cracking of lips; injection of both bulbar conjunctivae.



August 24: In the morning he had a fever of 38.8°C, and at night it was 40°C. He received an intramuscular injection of chloromycetin.

August 25: In the morning he had a fever of 39°C and at night it was 40°C. He had right cervical adenopathy as big as a chicken egg. The lymph node was hard and painful to the touch. He also had erythema on his palms and soles.

August 26: Both hands and feet were very red and edematous. His lips were dry, red and fissured. Body temperature was 39–40°C.

August 27: He had bilateral ocular conjunctival injection. His erythema was localized in both hands and feet, especially the palms and soles, which were edematous. His body temperature was 39–40°C. He received an injection of promethazine hydrochloride.

August 28: He had a rash not only on his hands and feet, but also had a rubella-like or urticaria-like rash on his abdomen, chest and back. Cervical lymph nodes became smaller. His body temperature was 39–40°C.

August 29: Right cervical lymph nodes became smaller, about the size of the tip of the thumb. He did not cry when the lymph node was touched. The rash became macular all over his body. His body temperature was 38–39°C.

August 30: High fever persisted. The primary doctor referred him to our department. He received an intramuscular injection of chloromycetin and oral Ilosone (erythromycin) syrup. He also received sulpyrine, VB2 and Pyrethia.

Physical examination on admission. He had bilateral ocular conjunctival injection. His lips were dry, congested, eroded and fissured. His oral cavity was diffusely red, and he had a strawberry tongue. However, there were no aphthae, ulcer or pseudomembrane. A right cervical lymph node was as big as the tip of the thumb and slightly firm. He had a rash over his entire body. In some places the rash was macular, while in other places it looked like scarlet fever. However, his hands and feet were the most obvious.

Clinical course in the hospital. See Temperature Chart 3.

August 31: Bilateral ocular conjunctiva injection almost resolved.

September 1: He had resolution of the rash except for a scarlet fever-like or macular rash on his back.

September 3: The rash resolved completely and cervical lymph node was no longer palpable.

September 4: Desquamation started from between the nail and the exposed skin at the tip of the finger of both thumbs and the left forefinger.

September 6: Lips and oral changes resolved.

September 9: Desquamation noted between the nail and the exposed skin at the tip of the big toes.

September 11: He was discharged with complete

WBC 12 300, left shift with metamyelocytes. Paul-Bunnet negative, Coombs test negative, blood culture negative, Tiselius showed gamma-globulin 22.9%. Cerebrospinal fluid (CSF) analysis almost in the normal range. Bacterial culture from a throat swab yielded normal flora. The urinalysis showed trace protein and a few RBC. However, there was no evidence of nephritis.

Therapy. The primary doctor treated him with chloromycetin palmitate syrup 750 mg/day from April 24 and penicillin 100 000 U from April 27 to 29. In the hospital he received intravenous chloromycetin succinate 1 g/day for the first 3 days. Then he was treated with Ilosone (erythromycin) syrup 600 mg/day orally and, beginning on April 2, intramuscular penicillin 900 000 U × 6 doses was added. There was no use of steroids in this patient.

Case 3: male, 8 months (Case 4). Admitted. August 30, 1965.

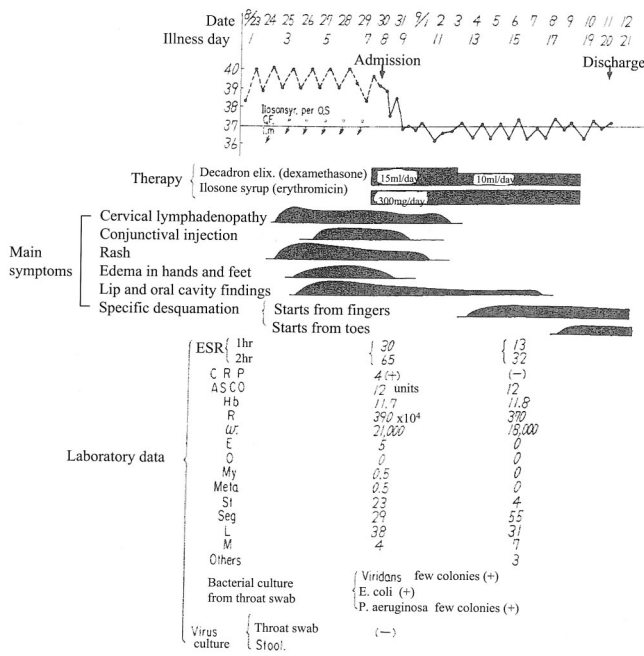
Discharged. September 11, 1965.

Chief complaint. Fever.

Family history. Father was in good health. Mother had frequent episodes of urticaria since childhood. Her skin tended to have eruptions when she used tape.

Past history. His weight at birth was 2400 g. He was fed formula and had normal growth. He had a slight rash. He could hold his head erect at 3 months and sit alone at 6 months.

Present history. August 23, 1965: In the morning he had a fever of 38.4°C and visited his primary doctor. He was diagnosed with pharyngitis (angina) by his doctor. That night he had a temperature of 40°C.



TEMPERATURE CHART 3.

recovery except for desquamation of the hands and feet.

Laboratory data. As shown in the chart, on admission his ESR was 30 mm/1 h, 65 mm/2 h, CRP 4 (+), ASLO 12 U, WBC 21 000 with left shift including myelocytes which returned almost to normal by September 6. Viral cultures of the throat and stool were negative (reported by Dr. Ashihara of the National Institute of Infectious Diseases).

Therapy. As shown in the chart, on admission he was started on oral Decadron syrup (dexamethasone) 15 cc (1.5 mg)/day and Ilosone (erythromycin) syrup 300 mg/day. His fever declined by the afternoon of the next day.

Case 4: male, 5 years 1 month (Case 26). Admitted. April 5, 1966.

Discharged. April 24, 1966.

Chief complaint. Fever, right lymphadenopathy.

Family history. Father had a history of urticaria. The patient's paternal grandmother had asthma. A paternal uncle had asthma and urticaria and his son (first cousin) suffered from severe asthma. The mother and older sister were healthy.

Past history. His weight at birth was 3600 g. He was fed formula with normal growth and development. He had no history of asthma or eczema.

Present history. March 30: At midnight he had right neck pain. He had a tactile fever, but it was not recorded with a thermometer.

March 31: He was seen by his primary doctor who diagnosed right cervical lymphadenitis. The neck pain persisted, and he did not allow people to touch his neck. He received Ilosone 600 mg and methylprednisolone

1.5 mg. He had a fever of 38.2°C in the morning, 38.0°C at noon and 37.9°C at night.

April 1: He did not want to eat anything and he had persistent neck pain. He had a fever of 37.8°C in the morning, 38.0°C at noon and 39.0°C at night.

April 2: He had a fever of 37.7°C in the morning and 39.0°C at noon. He received an antipyretic, and he had a fever of 37.0°C at night. His right neck pain persisted.

April 3: Bilateral ocular conjunctival injection was noted in the morning. He also had dry, red, eroded and fissured lips. His forehead and both auricles had an erythematous macular rash. He had erythema on both palms and soles by around noon. He also had severe headache, and he vomited even water. He had a fever of 38.2°C in the morning, 38.2°C at noon and 38.6°C at night.

April 4: His right cervical lymphadenopathy improved. He still had severe headache and vomiting. He had a fever of 39.0°C in the morning, 38.7°C at noon and 39.0°C at night.

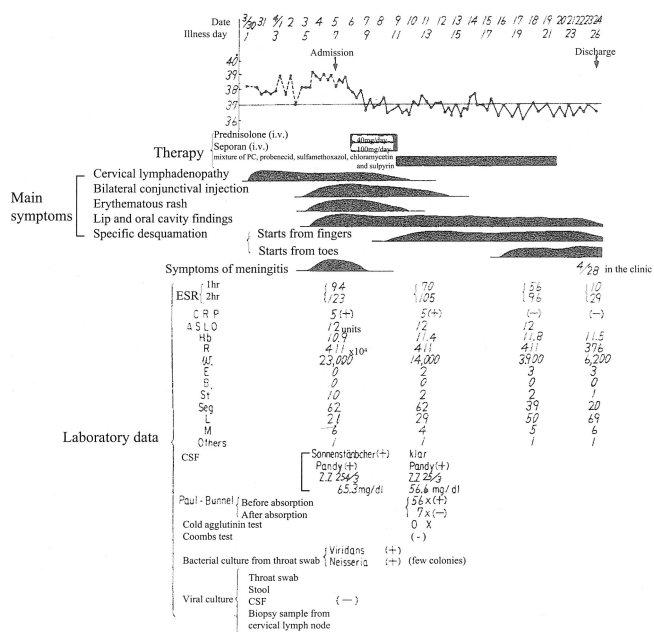
April 5: He had a fever of 39.5°C in the morning. He developed a new macular erythema on his chest and back. He had severe headache. The primary doctor referred him to the pediatric department in Japan Red Cross Hospital.

Physical examination on admission. The patient appeared to be in pain. He had obvious bilateral ocular conjunctival injection. His right cervical lymph node was the size of a quail egg, and it was hard and painful. His lips were dry, red, eroded and fissured. His oral cavity was diffusely injected. He had a strawberry tongue. As shown in Figure 3 erythema was prominent on the auricles, hands and soles. There was a clear demarcation between healthy skin and the macular erythema on the dorsa of the hands and feet. There was also erythema on the chest and back. A measles-like rash was scattered on the extensor surface of both legs. He had brisk patellar reflexes bilaterally and neck stiffness. Brudzinski's reflex was positive, but the Babinski sign was negative.

Clinical course in the hospital. See Temperature Chart 4.

April 5: His CSF was analyzed immediately after admission. Analysis showed Pandy (+), WBC 254 cells/3 hpf [high power field], glucose 65.3 mg/dl, which suggested aseptic meningitis.

April 6: He had bleeding from his fissured lips with crusting. Dr. Kajigaya, who was the surgeon at Futonaka Surgical Clinic, attempted to excise the swollen cervical lymph node. However, since the swollen lymph node was deep below the sternocleidomastoid muscle, he excised two rice-sized subcutaneous lymph nodes instead. A histologic examination and a viral culture were performed on these lymph nodes. Simultaneously a skin biopsy of the macular erythema was also performed.



TEMPERATURE CHART 4.

April 7: The rash resolved except for slight redness over the small joints of the fingers and slight erythema on both palms.

April 9: The rash disappeared. Desquamation started from between the nail and the exposed skin at the tips of all the fingers.

April 10. A drug challenge test was performed. The patient received a mixture of penicillin G 400 000 U, probenecid 0.5 g, Sinomin (sulfamethoxazole) 0.3 g, chloromycetin 400 mg, sulpyrin 0.6 g and sulfisomidine (sulfa) 1.0 g per day.

April 12: Bilateral ocular conjunctival injection nearly resolved.

April 16: Desquamation started from between the nail and the exposed skin at the tip of the left first toe. There was no apparent reaction to the drug challenge.

April 24: The changes in the oral cavity and lips almost disappeared. He recovered completely except for desquamation of both hands and feet and was discharged.

Laboratory data. The laboratory data on admission were as follow: ESR 94 mm/1 h, 123 mm/2 h, CRP 5 (+), ASLO 12 U, WBC 23 000 with 10% stab cells (band forms) and a slight left shift. CSF examination showed dust-like turbidity (+), Pandy (+), WBC 254 cells/3 hpf (most cells were monocytes), and glucose 65.3 mg. The CSF improved rapidly, and an analysis on April 11 showed 25 WBC/3 hpf. Paul-Bunnell test was negative. Cold agglutinin test negative, Coombs test negative. ECG [electrocardiograph; EKG] was normal.

Therapy. The patient received intravenous prednisolone 40 mg/day and sevoran 1 g, along with other medications beginning on April 6. Many of his symp-

toms disappeared and his general condition improved within 3 days, so these medications were stopped. After that he recovered well. His drug challenge test was negative.

Case 5: male, 1 year 2 months (Case 42). Admitted. May 18, 1962.

Discharged. June 7, 1962.

Chief complaint. Fever.

Family history. The father had a history of urticaria. The paternal grandfather had asthma. The mother was healthy.

Past history. He had a normal birth and normal growth. He was fed formula. He did not have any eczema during infancy.

Present history. May 14, 1962. He had a fever of 37.9°C in the morning. An otolaryngologist diagnosed otitis media. He had slight rash on his right neck. He had a fever of 39°C in the evening.

May 15: He had fever of 38.0–39.2°C and a macular rash on his hands and feet.

May 16: His lips and oral cavity appeared inflamed. He had a fever of 38.2–39.2°C.

May 17: He developed bilateral conjunctival injection. He had a fever of 39.0–39.5°C.

May 18: He was hospitalized with a chief complaint of high fever.

Physical examination on admission. As shown in Figure 4, he had an obvious macular rash on the hands and feet, which were edematous. Erythema was noted on the neck, external genitalia and perianal region. He had bilateral conjunctival injection. His lips were dry, red, eroded and fissured. The mucosa of oral cavity was inflamed. He also had strawberry tongue. However, he did not have cervical lymphadenopathy or generalized lymphadenopathy. He did not have pharyngitis.

Clinical course in the hospital. See Temperature Chart 5.

May 18: Erythromycin and penicillin were administered for 3 days, but the fever persisted.

May 21: Oral prednisolone 10 mg/day was started.

May 22: His temperature was 37.6–38.0°C. Almost all clinical symptoms resolved.

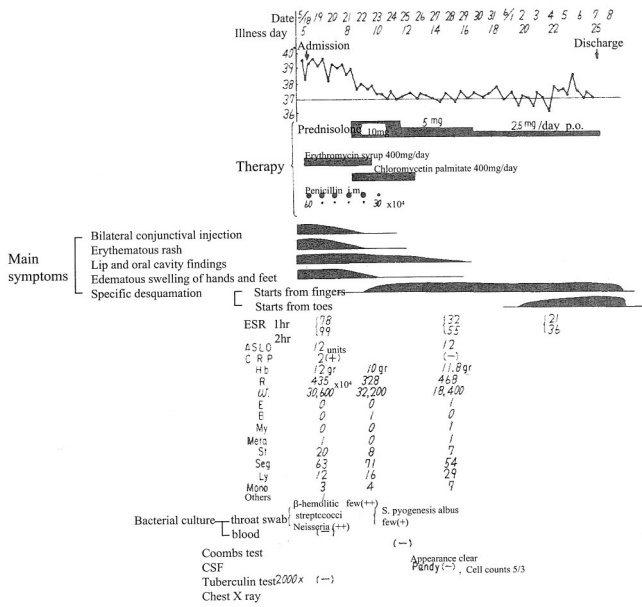
May 23: Desquamation started from between the nail and the exposed skin at the tip of the right thumb (Illness Day 11).

June 2: Desquamation also noted on his toe.

June 7: The desquamation of his hands and feet continued. He recovered completely and was discharged.

Laboratory data. On admission laboratory data were as follows: ESR 78 mm/1 h, 99 mm/2 h. Hgb 12 g, RBC 4 350 000, WBC 30 600 with eosinophils 0%, metamyelocytes 1%, stab cells 20%, segmented neutrophils 63%, lymphocytes 13%, monocytes 3%, others 1%. CRP 2 (+), ASLO 12 U. A blood culture was sterile. Coombs

Case #5. Male, 1yr.2 mos., hospitalized 5/18-6/7/62



TEMPERATURE CHART 5.

test was negative. The culture from a throat swab showed *Neisseria* (++) , beta-streptococcus (+).

This was a case who did not develop cervical lymphadenopathy.

Case 6: female, 1 year 7 months (Case 10).

Admitted. November 4, 1964.

Discharged. November 16, 1964.

Chief complaint. Fever, poor appetite.

Family history. Father and mother were healthy.

There was no family history of allergy. There was no history of eczema during infancy.

Present history. October 27, 1964: She was not doing well all morning and she suddenly had a seizure around noon. At that time she had a fever of 40°C; cough (-), coryza (-), nasal discharge (-).

November 1: Her lips appeared eroded.

November 2: She had a fever of 39.3°C. Bilateral conjunctival injection was noted. Her primary doctor noted left cervical lymphadenopathy.

November 3: She developed edematous hands and feet with a fever of 39°C.

November 4: She was admitted to our pediatric department.

Physical examination on admission. She did not have a rash on her body. She had obvious bilateral conjunctival injection. Her lips were red, eroded, fissured and dry. Her tongue was flat and glossy. It was not like a strawberry tongue. The mucosa of the oral cavity was diffusely injected. There were no aphthae or pseudomembrane. On the left side of the neck and below angle of the mandible, there was a lymph node about the size of the head of the thumb. It was firm and painful, but there was no overlying erythema. The

patient had marked edema of the dorsa of the hands and the palms.

Clinical course in the hospital. See Temperature Chart 6.

November 5: The bilateral conjunctival injection and edema of the hands resolved. She became afebrile.

November 10: Desquamation started from between the nail and the exposed skin at the tip of the right thumb.

November 11: She still had eroded and fissured lips.

November 16: She recovered almost completely and was discharged. She had slight desquamation on her fingers.

Laboratory data. November 5: ESR 34 mm/1 h, 73 mm/2 h. *Pseudomonas aeruginosa* (+) grew from a throat swab. Hematologic examination showed Hgb 11 g/dl, RBC 3 750 000, WBC 12 500 with eosinophils 1.5%, myelocytes 0.5%, metamyelocytes 0.5%, stab cells 10%, segmented neutrophils 56%, lymphocytes 27%, monocytes 4%, others 5%. CRP 2 (+), ASLO 12 U. Cold agglutinin reaction was 1:16. Coombs test was negative. Paul-Bunnell test was negative. This is a female case who did not have a rash but had desquamation from between the nail and the exposed skin at the tip of the finger. She was not so severely ill, so she was observed without any medication in the hospital.

Case 7: female, 2 years 4 months (Case 15).

Admitted. August 25, 1966.

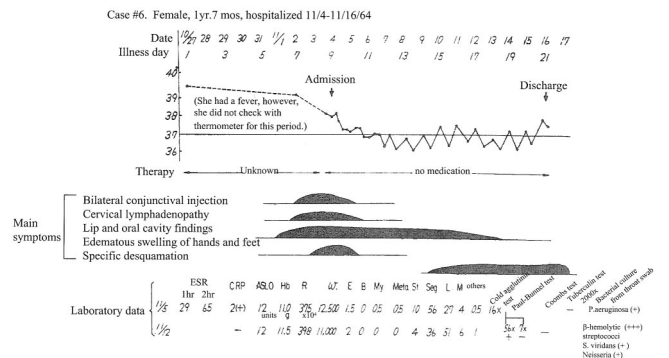
Discharged. September 6, 1966.

Chief complaint. Fever, rash.

Family history. The father had a history of skin rash following exposure to certain products. The mother was healthy. The patient had a monozygotic twin sister and an older sister age 5 years. Both were healthy.

Past history. Her weight at birth was 1600 g. She was fed formula. She did not have eczema during her infancy. She held her head erect at 4 months and walked alone at 1 year 6 months. She caught colds often but she did not have wheezing.

Present history. August 21, 1966: She became inactive in the late afternoon and appeared ill. She had a tactile fever, but it was not recorded with a thermom-



TEMPERATURE CHART 6.

eter. She had right neck pain. Her mother noticed she had right cervical lymph node swelling (about 7 p.m.).

August 22: She had a fever of 38.2°C in the morning. She visited her primary doctor who was a surgeon. The doctor diagnosed cervical lymphadenitis. Later, she had a fever of 39.4°C.

August 23: She had a fever of 38.2°C in the morning. She visited the primary doctor who was an otolaryngologist. He diagnosed lymphadenitis and ruled out otitis media. She had a fever of 37.6°C at noon and 39.9°C at 8 p.m. She visited the pediatric primary doctor.

August 24: Her temperature was 37.2°C in the morning and she played outside. She had a fever of 38.4°C at night and a macular rash on her hands and feet about 10 p.m. At the same time she was noted to have bilateral conjunctival injection.

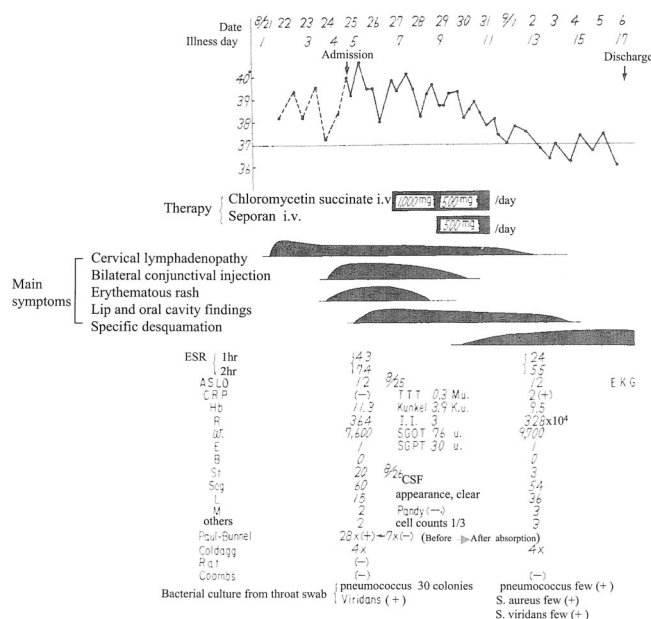
August 25: She had a fever of 40°C. She either cried unhappily or slept. She had mouth pain. She had erythema not only on her hands and feet but also on her body. Her primary doctor referred her to our department.

Physical examination on admission. She looked normal size for her age. She had obvious bilateral conjunctival injection. Her lips were dry, red, eroded and fissured. The mucosa of her oral cavity was diffusely congested. Her throat was obviously red, but there was no pseudomembrane, ulcer or aphthae. Her tongue was coated but in some places had swollen papillae as in the so-called strawberry tongue. A right cervical lymph node was as big as a quail egg. It was firm and painful to the touch. There was no overlying erythema. A macular rash was noted over the body and especially on the palms and soles. The rash was not vesicular. She had a normal examination of the lungs and heart. Her liver and spleen were not palpable. Her external genitalia and perianal region were normal.

Clinical course in the hospital. See Temperature Chart 7.

August 25: ESR 43 mm/1 h, 74 mm/2 h, CRP (-), ASLO 12 units, RA [rheumatoid arthritis] test (-), cold agglutinin reaction 1:4, Paul-Bunnell test negative. Liver tests revealed an icteric index of 3, SGOT [aspartate aminotransferase, AST] 76, SGPT [alanine aminotransferase, ALT] 30, TTT 0.3 μU, Kunkel 3.9 KU. Hematologic examination showed Hgb 11.3 g/dl, RBC 3 640 000, WBC 7600: eosinophils 1%, stab cells 20%, segmented cells 60%, lymphocytes 15%, monocytes 2%, others 2%. *Streptococcus pneumoniae* (30 colonies) and a few colonies of *Streptococcus viridans* grew from a throat swab. Urinalysis was normal.

August 26: A skin biopsy was performed on the erythematous rash on her right middle finger and on her buttocks. Examination of the CSF was normal; appearance clear, Pandy (-), WBC 1/3 hpf. Bilateral



TEMPERATURE CHART 7.

conjunctival injection and macular rash started to disappear.

Throat swab, stool and CSF (total, eight samples) were collected from August 25 to 27 and cultured for virus by Dr. Ashihara of the National Institute of Infectious Diseases.

August 28: The rash almost disappeared. Her high fever persisted.

August 29: The bilateral conjunctival injection disappeared.

August 30: The lips were still obviously dry, eroded and fissured. The right cervical lymph node shrank to the size of the tip of the thumb and became firm. The rash completely resolved. Desquamation started from between the nail and the exposed skin at the tip of the right thumb.

August 31: Characteristic desquamation was seen on the tip of almost all fingers of the right hand.

September 1: Her temperature decreased to 37–38°C.

September 2: Her lips improved. The right cervical lymph node was barely palpable.

September 3: Desquamation was also seen from between the nail and the exposed skin at the tip of the right first toe.

September 6: She still had desquamation of her fingers and toes; however, she recovered almost completely and was discharged.

Laboratory data. Laboratory data on August 25 as shown above. The laboratory data on September 2 (Illness Day 13) showed ESR 24 mm/1 h, 55 mm/2 h. CRP 2 (+). ASLO 12 U. Cold agglutinin reaction 1:4, Coombs test negative. Hematologic examination showed Hgb 9.5 g/dl, RBC 3 280 000, WBC 9700, eosin-

ophils 1%, stab cells 3%, segmented cells 54%, lymphocytes 36%, monocytes 3%, others 3%. Throat culture grew *Staphylococcus aureus*, few colonies (+); *S. pneumoniae*, few colonies (+); and *S. viridans*, few colonies (+).

September 6: She had a prolonged PQ on her ECG examination. She was followed without any medication and was checked on December 8, 3 months after discharge. She was healthy, and the ECG was completely normal at that time.

The results of virus cultures are still pending.

Therapy. We observed her without any medication on August 25 and 26. She received intravenous chloromycetin 1 g/day starting August 27. She received both chloromycetin 0.5 g/day and Seporan 0.5 g/day beginning on August 29.

August 31: All medication was discontinued. Steroid hormone was not used at any time.

SYMPTOMATOLOGY OF OUR 50 CASES

The cases can be divided into two groups based on the presence or absence of cervical lymph node swelling, which is one of the major symptoms among our cases. The first group had lymph node swelling that was bigger than the head of the thumb and in some cases even larger than a chicken egg. We tentatively named this group the “cervical lymphadenopathy +” (CLA+ group). The second group did not have lymph node swelling, and we called them the CLA- group. I organized the patients into these two groups according to age (Table 1). Thirty-three cases numbered 1 to 33 belong to the CLA+ group. Seventeen cases (Cases 34 to 50) belong to the CLA- group. The clinical analysis of this syndrome will be presented for all 50 cases, which is a combination of the CLA+ and CLA- groups. I will point out the differences between these two groups when appropriate.

1. Regional distribution. As depicted in the figure, we did not see any relationship between the cases or epidemics of the syndrome.

2. Family history of allergy (Table 2). A high tendency to have urticaria was reported among the parents.

3. Incidence by year and season (Table 3). The number of cases increased dramatically beginning in 1962. I am not sure if this was due to a true increase in cases or increased case ascertainment. If you look at the seasonality, October, November, December and February have a lower incidence. As a general trend the number of cases was higher in the spring and summer and lower in the autumn and winter.

4. Age distribution (Table 4). More than one-half of the cases (54%) were infants under the age of 2 years. The age distribution ranged from 2 months to 9 years 1 month. Only five cases (10%) were over 6 years

Geographic distribution



Geographic distribution of the patients by year

Year	Japan Red Cross Hospital located in Shibuya													Total										
	Shibuya	Suginami	Meguro	Minato	Itabashi	Soka	Setagaya	Kawasaki	Kitatama	Irima-Cun	Nakano	Taito	Nerima		Shinjyuku	Bunkyo	Toshima	Kawaguchi	Musashino	Warabi	Machida	Fucyuu	Yokohama	
1961																								1
1962	3	1	1	1			1					1												9
1963	1	1	1	1	1									1										7
1964	1	1					1	1							1	1				1				7
1965	3	2				2				1	1							1						10
1966	2	2	2					1									1				1	1	1	16
Total	10	7	4	3	3	2	2	2	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	50

[Regional distribution of Kawasaki syndrome.]

old. Therefore we conclude that this syndrome is mainly one of infants.

5. Gender distribution (Table 5). There were 32 boys and 18 girls. The gender ratio of ~5 boys to 3 girls suggests a higher incidence among boys.

6. Analysis of the presenting symptoms and chief complaint (Table 6). The signs and symptoms described during hospitalization are based on the medical record; thus I think they are accurate. However,

Table 2. Family history of allergy (46/50 cases).

		Bronchial asthma	Urticaria	Rash caused by drug allergy	Eczema or atopic dermatitis	Strophulus
Paternal side	Grandfather		1	1		
	Grandmother	2	1			
Maternal side	Grandfather					
	Grandmother					
Father		1	12	3	3	
Mother			10	3	1	
Siblings of father		1	2			
Siblings of mother		1		1		
Sibling of patients				1	3	
Patient						
In infancy				1	13	
After infancy						2

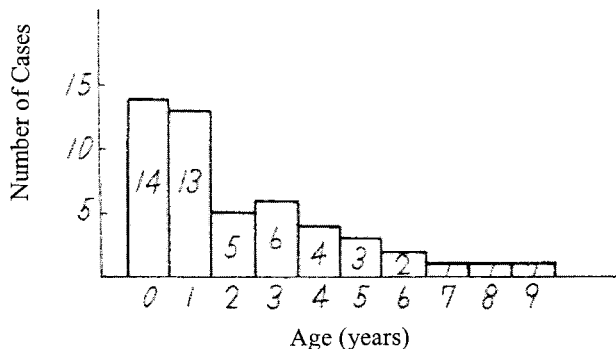
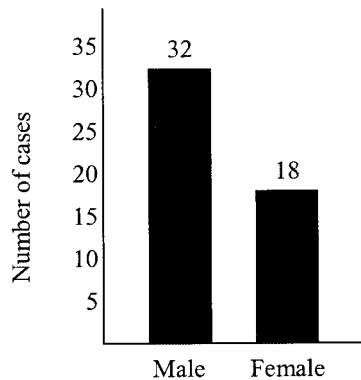
Table 3. Incidence by year and season.

	Jan	Feb	Mar	Apr	May	Jun	July	Aug	Sep	Oct	Nov	Dec	Total
1961	1												1
1962				1	3	1	2		1		1		9
1963	1	2	2	1								1	7
1964			1	1		1	1	1	1		1		7
1965			1		2	2	1	3	1				10
1966	2		2	1		1	4	2	2	2			16
Total	4	2	6	4	5	5	8	6	5	2	2	1	50

Table 4. Age distribution

Age (yrs.)	0	1	2	3	4	5	6	7	8	9	10	Total
CLA (+)	6	8	2	5	4	3	2	1	1	1	0	33
CLA (-)	8	5	3	1	0	0	0	0	0	0	0	17
Total	14	13	5	6	4	3	2	1	1	1	0	50

Table 5. Sex : Male 32 cases, Female 18 cases



the symptoms and signs before hospitalization are based on whatever the family members, mainly the mother, told us. Therefore these reports may not be accurate. A few cases had reports of their disease course prepared by a physician, in which case we can expect greater accuracy. Some mothers wrote down the pattern of fever, but others answered questions only from memory. Thus the temperature chart for each case, as described later in the section on treatment, is based on the information as described above. For patients less than 2 years of age, rectal temperatures were used.

Presenting symptoms (Table 6-1). Most cases began abruptly with the onset of fever. Prodromes included neck pain (four cases), cough (two cases), cervical lymph node swelling (one case), whining (one case) and abdominal pain (one case). This suggests that "common cold-like" prodromes were absent in most cases.

Chief complaint (Table 6-2). Fever was by far the most frequent chief complaint at the time of hospital-

ization or at the first visit (48 cases, 98%). These patients experienced persistent high fever in spite of treatments prescribed by their family doctors and were therefore referred to our hospital. The next most common chief complaints were rash, followed by cervical lymph node swelling and red eyes.

Diagnoses made by other physicians (Table 6-3). Although there was a variation in the diagnosis made by the physicians who initially evaluated the patients, most were diagnosed in the early stage of the illness as common cold, lymphadenitis or pharyngitis and in the later stage as mumps, measles, scarlet fever or sepsis. It is interesting to see the variety of diagnoses, which reveals the complexity of this syndrome.

Illness day at admission (Table 6-4). Most of the cases were hospitalized between the third and ninth illness day. The majority were hospitalized between Illness Days 4 and 6, probably because the main symptoms, like rash and injection of the bulbar conjunctivae, occurred at this time. With the advent of these signs, the doctors treating these patients realized that this was not a common disease and referred the patient to us.

7. Main clinical symptoms (Table 7). The main clinical symptoms of this syndrome are listed in Table 7. I will describe each symptom in detail.

a. Fever (Tables 8 to 12). One of the most important symptoms of this syndrome is fever. High fever above 38°C or as high as 41°C and lasting longer than 6 days was observed in all the cases. In 46 cases (92%) the peak temperature was above 39°C. In only four cases did the temperature remain between 38 and 38.9°C (Table 8). The duration of the fever above 38°C was 6 to 20 days but usually <15 days (Table 9). Some cases had low grade fever between 37°C and 38°C for a relatively long period.

The duration of hospitalization and the day of illness at discharge were related to the fever and other laboratory data. As shown in Table 10 the duration of the hospitalization was ~9 to 30 days and the illness day at discharge was between the 16th and 35th days, with some exceptions (Table 11). I thought that the duration of fever might be influenced by the treatment, especially steroids, so I compared the duration of fever between cases treated with steroids (22 cases) and without steroids (28 cases). There was no significant difference between the 2 groups. Despite this I had the clinical impression that in certain cases the fever or

Table 6. First symptoms at onset
6.1)

Symptoms at onset	No. of cases
Fever	43
Irritability	7 (1)
Neck pain	6 (4)
Cervical lymphnode swelling	4 (1)
Cough	3 (2)
Sore throat	2
Poor appetite	2
Nasal discharge and obstruction	1
Nausea and vomiting	1
Abdominal pain	1 (1)

The number in () indicates the number of the cases who presented with the symptom prior to the onset of fever.

6.2) Analysis of chief complaint

Chief complaint	No. of cases
Fever	48
Rash	19
Cervical lymphnode swelling	11 (1)
Red eyes	6
Poor appetite	3
Inactive, unwilling to walk	1 (1)
Nasal obstruction	1
Diarrhea	1
Somnolence	1

The number in () indicates the number of cases who did not complain of fever.

6.3) Diagnosis of other doctors (by doctors previous to hospital evaluation)

Diagnosis of other doctors	No. of cases
Cervical lymphadenitis	12
Pharyngitis	6
Measles	5
Common cold	9
Scarlet fever	3
Mumps	3
Sepsis	2
Rubella	2
Strophulus	1
Aspirin rash	1
Drug rash	1
Rheumatic fever	1
Pharyngo-conjunctivitis	1
Otitis media	1
Auto-toxicosis	1
Izumi fever	1
Meningitis	1
Allergic disease	1
Viral infection	1

6.4) Illness day at hospitalization

Illness day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Total
No. of cases	0	0	3	11	11	11	4	5	2	0	1	0	0	0	0	2	0	0	50

Table 7. Main clinical symptoms

Symptoms	No. of cases (%)
1) Persisting fever (>38°C) more than 6 days	50 (100%)
2) Cervical lymph node swelling (bigger than the tip of the thumb)	33 (66%)
3) Bilateral congestion of bulbar conjunctiva	49 (98%)
4) Erythematous rash of skin	43 (86%)
5) Vaso-neurogenic edematous-like swelling of hands and feet bilaterally	22 (44%)
6) Erosion or cracking of lips, diffuse congestion of oral mucosa, sometimes strawberry tongue	48 (96%)
7) Membranous desquamation from nail beds of fingers and toes	49 (98%)

Table 8. The highest body temperature and case number

Body temperature	≥ 40°C	39°-40°C	38°-39°C	Total
No. of cases	22	24	4	50

The rectal temperature was measured for the patients under the age of two during hospitalization.

clinical symptoms were greatly improved by steroid treatment. It may be that simply looking at the effect of steroids on duration of fever is not the best way to judge its efficacy. On the other hand Table 9 indicates that this syndrome heals itself very well even without treatment with steroids. The 8 cases with recurrent fever (Table 12) were more likely to have been treated with steroids than the cases without recurrent fever. These recurrent fever cases had only fever without rash or conjunctival injection.

Table 9. Comparison of the duration of persistent fever (≥ 38°C) with and without steroid treatment.

Duration of fever (days)	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	31	Total
Steroid (+)	3	1	5	5	1	2	1	0	1	0	0	1	1	0	0	0	1	22
Steroid (-)	2	5	4	7	3	2	2	1	0	1	0	0	0	0	1	0	0	28
Total	5	6	9	12	4	4	3	1	1	1	0	1	1	0	1	0	1	50

For details of the fever pattern, refer to the fever curves in the individual case reports in the treatment section.

b. Cervical lymph node swelling (Tables 13 to 18; Photographs 1, 4 and 17). One of the characteristics of this syndrome is deep lymph node involvement with the most frequent being the lymph node under the sternocleidomastoid muscle in the submandibular region. It can develop to the size of the head of the thumb or can be even the size of a chicken egg. The lymph node mass is firm to palpation. There is no overlying erythema or warmth. Usually the lymph node enlargement is quite painful (Table 13). Torticollis caused by pain was observed often. It was unilateral in most cases, but either side of the neck was affected equally (Tables 14 and 15). Lymphadenopathy often developed on the first or second illness day, which suggests that this syndrome may have a pathology related to cervical

Table 10. Duration of hospitalization (days) and number of cases

Duration of hospitalization (days)	6	9	11	12	13	14	15	16	17	18	19	20	21	24	25	26	27	28	29	36	38	81	Total
Number of cases	1	2	2	1	4	2	3	3	4	3	2	3	8	2	2	1	1	1	1	2	1	1	50
Total	12			26						7				5			50						

Table 11. The disease day of discharge and number of cases

Illness day at discharge	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	32	33	34	40	41	53	88	Total
Number of cases	2	2	1	6	5	2	6	2	5	2	3	2	0	2	2	2	1	1	1	1	1	1	50
Total	18				20					12				50									

Table 12. Cases with recurrent fever (8 cases)

Case #	Age	Illness Day at the end of 1st fever	Illness Days of the 2nd fever	Illness Days of 3rd fever	Illness Day at discharge	Comment
5	10m	12	18, 19 (39-40°C)	23, 27 (38-39°C)	40	rectal temperature, steroid (+)
12	1y6m	9	11, 12, 13, 14 (38-40°C)		18	axillary temperature, steroid (+)
35	3m	11	23-32 (37.5-38.2°C)		32	rectal temperature, steroid (+)
19	3y6m	7	12, 13, 14, 15, 16, 17 (38-39°C)		32	axillary temperature, steroid (+)
40	11m	8	13, 14, 15, 16, 17 (38-37°C)	22, 23, 24, 25 (37.8-37.9°C)	26	rectal temperature, steroid (+)
45	1y10m	6	14, 15, 16 (38-39°C)	20, 21, 22, 23 (39-40°C)*	25	rectal temperature, steroid (-), otitis media*
46	1y11m	11	23, 24, 25 (38-39°C)		30	rectal temperature, steroid (-)
48	2y3m	9	12, 13, 14, 15, 16 (38-40°C)		21	axillary temperature, steroid (-)

Table 13. The size of cervical lymphadenopathy (at the time of hospitalization)

Size	Bigger than chicken egg	Wild brown chicken egg	Quail egg	Tip of the thumb	Total
No. of cases	14	3	5	11	33



PHOTOGRAPH 1. Case 15. Right cervical lymph node swelling, bilateral congestion of bulbar conjunctiva, and red, dry, eroded, partially cracked lips.

lymphadenitis. The duration of the lymph node mass was analyzed only in the cases with precise records (Tables 16 and 17).

Initially I divided the cases into CLA+ and CLA- groups. There is a clear difference in the age distribution between the 2 groups (Table 18). The ratio of infants under the age of 2 years was 14 of 33 cases (42.4%) in the CLA+ group vs. 13 of 17 cases (76.5%) in



PHOTOGRAPH 4. Case 22. Left cervical lymph node swelling, congestion of lips and both pinnae.

Table 14. The location of cervical lymphadenopathy

Location	Unilateral right	Unilateral left	Bilateral	Total
No. of cases	13	13	7	33

Table 15. Illness Day of cervical lymphadenopathy presentation

Illness Day	1	2	3	4	5	6	7	8	9	10	Total
No. of cases	11	10	4	2	4	0	1	1	0	0	33

Table 16. Illness Day of resolution of cervical lymphadenopathy (26 cases with relatively clear description)

Illness Day	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Total
No. of cases	1	1	3	1	1	3	5	5	4	1	1	0	0	0	26

Table 17. Duration of cervical lymphadenopathy (22 cases with relatively clear description)

Illness Day	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Total
No. of cases	2	1	0	2	2	4	2	2	3	2	1	1	0	0	22

the CLA- group, suggesting that lymphadenopathy was more common among the older patients. Even in the CLA- group, 8 cases were recognized to have small palpable lymph nodes the size of an azuki bean, a grain of rice, a soybean or less than the tip of the baby finger in the cervical region or other regions (axilla, groin or occiput). They are classified as CLA- because the lymph node swelling was not as obvious as in the CLA+ group. Node aspiration was attempted on cervical lymph nodes in 5 cases, but no fluid was recovered. Blood from the needle tip was cultured, but no bacteria were identified. The characteristic of the lymphadenitis in this syndrome is that it never suppurates. In 33 cases none of the nodes suppurated. Histologic examination was performed on 3 cases (Cases 1, 6 and 26) and will be described elsewhere. A portion of each biopsy sample was sent to Dr. Ashihara for viral

Table 18. Relationship between age and presence of cervical lymphadenopathy

Age (yrs.)	0	1	2	3	4	5	6	7	8	9	10	Total
No. of cases in CLA (+) group	6	8	2	5	4	3	2	1	1	1	0	33
No. of cases in CLA (-) group	8	5	3	1	0	0	0	0	0	0	0	17

isolation, but no viruses were isolated. Pathologic and microbiologic analyses (bacterial and viral isolation, immunofluorescent staining) of these lymph nodes are important, and I want to pursue these investigations in the future.

c. *Bilateral injection of the bulbar conjunctivae* (Table 19 and Photographs 16 and 19). To describe it more precisely, I should call it dilatation of capillary blood vessels in the bulbar conjunctiva. As shown in the photographs, each dilated blood vessel can be individually distinguished. Capillary congestion is not seen. No or little ocular discharge is present. In the opinion of the Chief Ophthalmologist, Dr. Kaji, "You can call this a simple conjunctivitis, but more likely this is a phenomenon that is part of a general vascular reaction along with the rash and other clinical findings."

Among the 43 cases with a reliable description, the most frequent timing of the appearance of this symptom was on the third to fifth illness day with disappearance by the end of the second week of illness (Table 19). The duration of the conjunctival injection varied, but most cases resolved within 10 days. This ocular symptom was a key finding for diagnosis and was recognized in 49 of 50 cases (98%). No complications such as formation of pseudomembrane, adhesions, corneal ulceration or other sequelae were observed.

d. *Rash* (Tables 20 to 23 and Photographs 5 to 12, 18, 20 and 21). The rash in this syndrome is mainly erythema, occasionally accompanied by a maculopapular rash like measles, rubella, scarlet fever, urticaria or rarely eczema, and the frequencies are shown in Table 20. Among the 43 cases with rash, 3 cases had a morbilliform rash only and 3 had a combination of a morbilliform and scarlatiniform rash. It should be noted that these 6 cases had no other erythematous rash. Although it is not noted in the table, I observed 2 infant cases with diffuse petechiae extending from the lateral aspect of both feet to the dorsum. I never observed frank purpura. The 7 cases without a recognizable rash developed specific skin peeling from the finger tips. Thus it is clear that they must have had a previous erythematous lesion of the finger tips. The

Table 19. Appearance, disappearance, and duration of bilateral congestion of bulbar conjunctiva (only obvious cases)

Appearance (Illness Day)	1	2	3	4	5	6	7						Total
No. of cases	3	6	8	14	9	2	1						43
Disappearance (Illness Day)	6	7	8	9	10	11	12	13	14	15	16	23	Total
No. of cases	4	2	7	4	5	5	4	4	5	1	1	1	43
Duration (days)	2	3	4	5	6	7	8	9	10	11	12	22	Total
No. of cases	1	5	6	6	4	3	4	3	4	1	1	1	39



PHOTOGRAPH 16. Case 26. Congestion of bulbar conjunctiva.

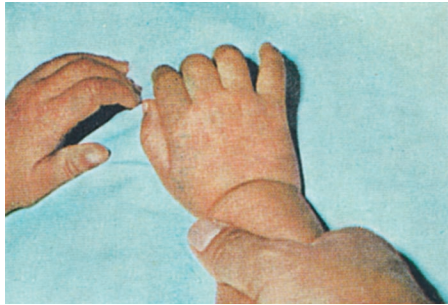


PHOTOGRAPH 19. Case 26. Congestion of bulbar conjunctiva (right side only) and catarrhal change of nares.



PHOTOGRAPH 5. Case 15. Typical erythema of the palm.

illness day at presentation of the rash (Table 21) was usually the third to fifth day, and it was very rare to develop rash after the second week of illness. The rash usually persisted for 1 week (Table 22), but it is important to note that in some cases the rash disappeared within 1 or 2 days. In terms of the distribution of the rash and its evolution (Table 23), most cases started with erythema of the extremities, especially the palms and soles, rather than starting on the face, neck or thorax. Often the erythema was limited to the palms, soles or fingertips. Thus the clinician must observe carefully. Sometimes I noted erythema overlying a finger joint or rash extending into the scalp. As



PHOTOGRAPH 6. Case 15. Erythema of the dorsum of the hand, especially prominent on and around the fingers.



PHOTOGRAPH 7. Case 15. Typical erythema of the soles.



PHOTOGRAPH 8. Case 15. Erythema of the dorsa of the feet, especially prominent on and around the toes.

described above, the characteristic rash of this syndrome is bilateral and symmetric, mainly on the palms and soles, and never forms vesicles or ulcers. Therefore it is called "multiforme" but not "exudativa."

e. Bilateral vasoneurogenic edematous swelling of the hands and feet (Photographs 22 to 25). As shown in the



PHOTOGRAPH 9. Case 15. Rash over the chest and abdomen.



PHOTOGRAPH 10. Case 15. Rash on the neck and the axilla.

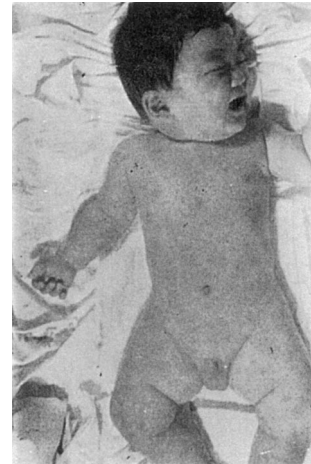


PHOTOGRAPH 11. Case 15. Rash on the nape of the neck and back.

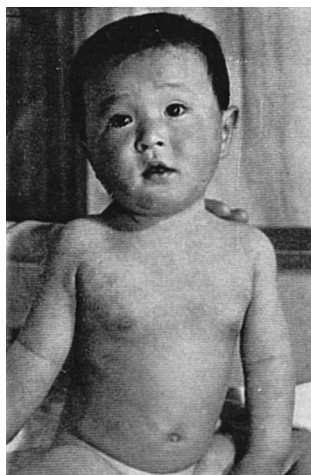
photographs, hands, feet and especially all the fingers and toes, palms and soles, and dorsa of the hands and feet swell so much that the skin becomes taut and shiny. This edema is nonpitting and was observed in 22 of 50 cases (44%). The finding was most common among the younger patients with 17 of 22 cases under



PHOTOGRAPH 12. Case 15. Rash over the waist and buttocks.



PHOTOGRAPH 21. Case 37. Rash over face, trunk and extremities (especially diffuse erythema of right hand).



PHOTOGRAPH 18. Case 39. Bilateral congestion of bulbar conjunctiva, erythematous rash over chest, abdomen and arms.



PHOTOGRAPH 20. Case 37. Erythematous rash over back and buttocks.

the age of 2 [years]. This finding was not necessarily associated with the presence of erythema of the hands and feet, so I described it as a separate symptom, even though the underlying pathophysiology may be identical.

Table 20. Characterization of the rash, the frequency in variation of rash, and rash combinations

Pattern of rash	No. of cases
Erythematous	12
Erythematous + measles or rubella-like	13
Erythematous + measles or rubella-like + scarlet fever-like	4
Measles or rubella-like	3
Scarlet fever-like + measles or rubella-like	3
Erythematous + scarlet fever-like	1
Erythematous + measles or rubella-like + urticaria-like	3
Erythematous + urticaria-like	2
Erythematous + scarlet fever-like + urticaria-like + sweat rash-like	1
Erythematous + sweat rash-like	1
No rash	7

Table 21. Illness Day of appearance of rash (only in the cases with clear description)

Illness Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total
No. of cases	4	3	10	10	6	4	2	0	0	0	1	0	0	0	40

Table 22. Duration of rash

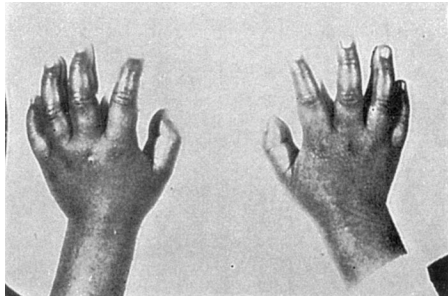
Illness Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total
No. of cases	4	2	3	2	6	9	6	1	4	1	1	0	1	0	40

Table 23. Order of appearance of rash

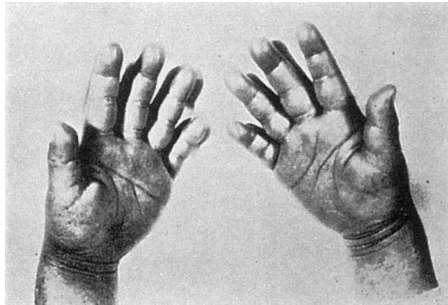
Appeared on extremities, especially palms and soles	29 cases (58%)
Appeared on chest, abdomen, back, face, or neck	14 cases (28%)
No rash (or not recognized)	7 cases (14%)

f. Symptoms of lips and oral mucosa (Photographs 1 to 3 and 17). The photographs demonstrate the dryness, redness, damage to the superficial epithelium, cracking and sometimes bleeding with eschars. One may see extreme and diffuse injection of the entire oral mucosa. However, it is characteristic that you will not see the formation of vesicles, pseudomembranes, ulcers or aphthae on the lips or oral mucosa. Sometimes the tongue may be covered with moss-like coating, but then, in most cases, it evolves into a strawberry tongue. I did not see any cases with exudative tonsillitis or pharyngitis at the time of hospitalization, although I have already described a number of cases diagnosed as pharyngitis by their first doctor at the time of disease onset.

These lip and oral cavity findings were recognized in virtually all cases (48 of 50, 97%). It is possible that



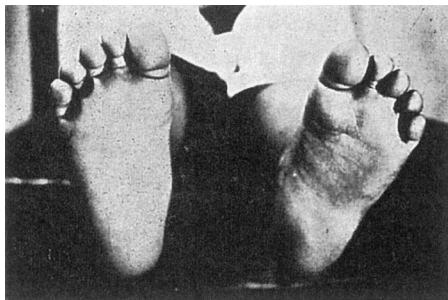
PHOTOGRAPH 22. Case 22. Vasoneurogenic, edematous swelling of the dorsa of both hands and all fingers.



PHOTOGRAPH 23. Case 22. Vasoneurogenic, edematous swelling of both palms and palmar side of fingers.



PHOTOGRAPH 24. Case 22. Vasoneurogenic, edematous swelling of the dorsa of both feet and all toes.



PHOTOGRAPH 25. Case 22. Vasoneurogenic, edematous swelling of both soles and plantar side of the toes.

these mucosal changes may also be related to dehydration as well as inflammation. As far as other mucosal symptoms, several cases had nasal discharge, but I am not sure about the exact numbers. There were almost no abnormalities of the anus or perineal area, except for one or two cases who presented with mild discharge.

g. Membranous desquamation from the junction of



PHOTOGRAPH 2. Case 26. Bilateral congestion of bulbar conjunctiva and red, dry, eroded, cracked lips.



PHOTOGRAPH 3. Case 14. Red, eroded, cracked lips; rash on both cheeks, head and chest.

the nail and skin on the fingers and toes (Tables 24 and 25 and Photographs 13 to 15 and 26 to 28). This very characteristic desquamation begins as a crack at the junction of the nail and skin on the tip of fingers, especially on the tip of the thumb. Shortly thereafter a small portion of skin starts to peel like a membrane. The initiation of peeling is generally the second week of

Table 24. Start of membranous peeling from nail bed of fingers and toes and no. of cases

Illness Day	No. of cases with peeling		Illness Day	No. of cases with peeling	
	Finger	Toe		Finger	Toe
1			17		1
2			18		5
3			19	1	5
4			20		2
5			21	1	
6			22		
7	3		23		1
8	2		24		1
9	4		25		1
10	8	1	26		
11	5	2	27		
12	6	1	28		
13	6	2	29		
14	4	3	30		
15	3	4	31		
16	2	2	Total	46 cases	31 cases

Table 25. The time interval (days) from the beginning of peeling on fingers to beginning of peeling on toes (analyzed for cases with clear description)

Days	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total
No. of cases	2	1	2	3	5	6	5	3	2	0	0	1	1	0	1	32 cases



PHOTOGRAPH 13. Case 15. Beginning of typical membranous desquamation from nail beds of fingers.



PHOTOGRAPH 14. Case 15. Typical membranous desquamation from nail bed of thumb.



PHOTOGRAPH 15. Case 30. Membranous desquamation at the tip of the toes; there is a scar from biopsy at the tip of the left second toe.

illness, in other words, from Illness Days 7 to 14. The following three patterns of desquamation were observed: (1) limited membranous desquamation only from the fingertip to the distal interphalangeal (DIP) joint; (2) membranous desquamation around the metacarpophalangeal (MCP) joint; (3) membranous desquamation around the wrist joint including both the dorsum and palm of the hand.

The pattern of desquamation on the toes and feet are almost same, but there were cases who presented with



PHOTOGRAPH 26. Case 15. Typical desquamation of the tips of all fingers.



PHOTOGRAPH 27. Case 37. Membranous desquamation of the fingertips.



PHOTOGRAPH 28. Case 11. Membranous desquamation of the tips of the toes.

peeling only on the finger tip but not on the foot. The peeling pattern of toes usually starts from the distal end of the toe, but initiation of peeling is usually later than that of the finger (Table 25) It is characteristic that membranous peeling is limited to the fingers, toes,