

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-acrodesquamatus 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,

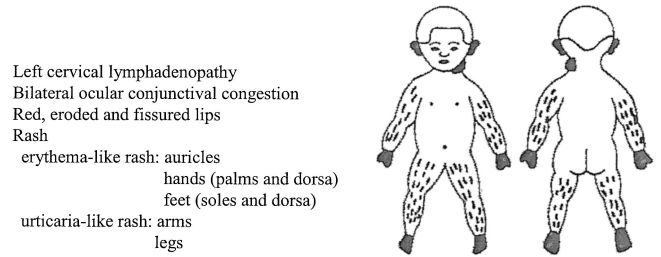


FIG. 1. Case 2 (1 year 8 months).

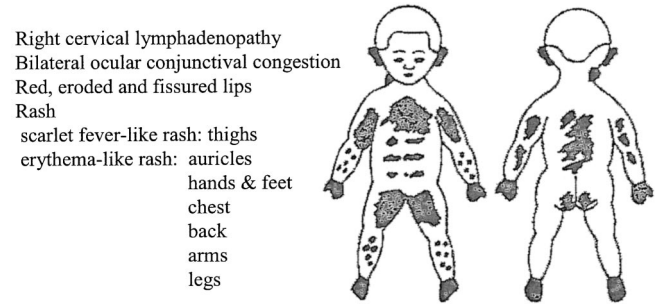


FIG. 2. Case 3 (8 months).

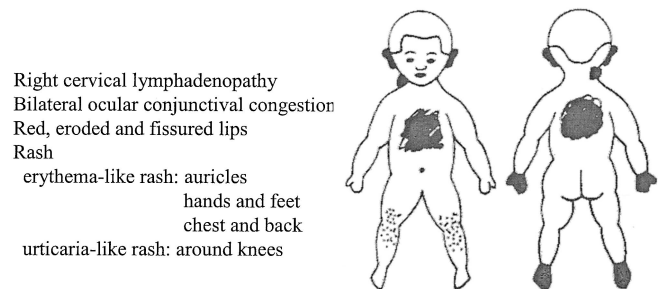


FIG. 3. Case 4.

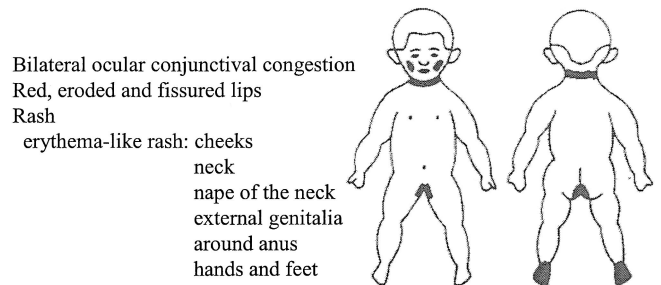


FIG. 4. Case 5 (1 year 2 months).

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.

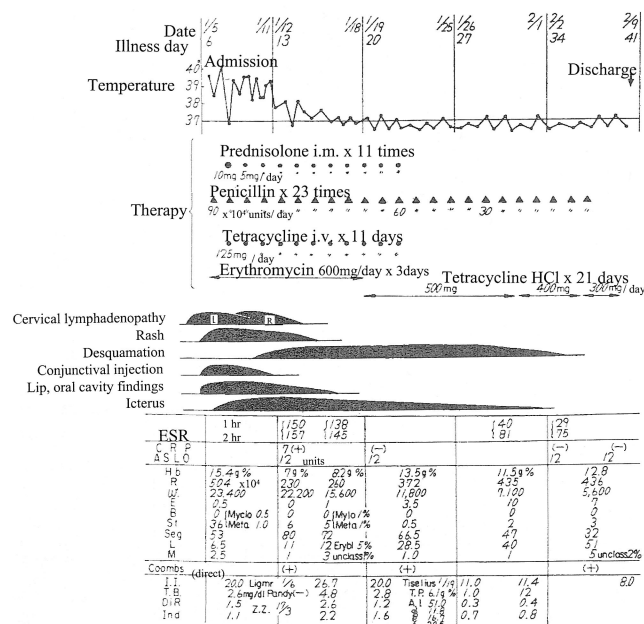
January 24: Patient smiled for the first time. Icterus of skin and bulbar conjunctive barely visible. Only the edge of liver was palpable.

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.

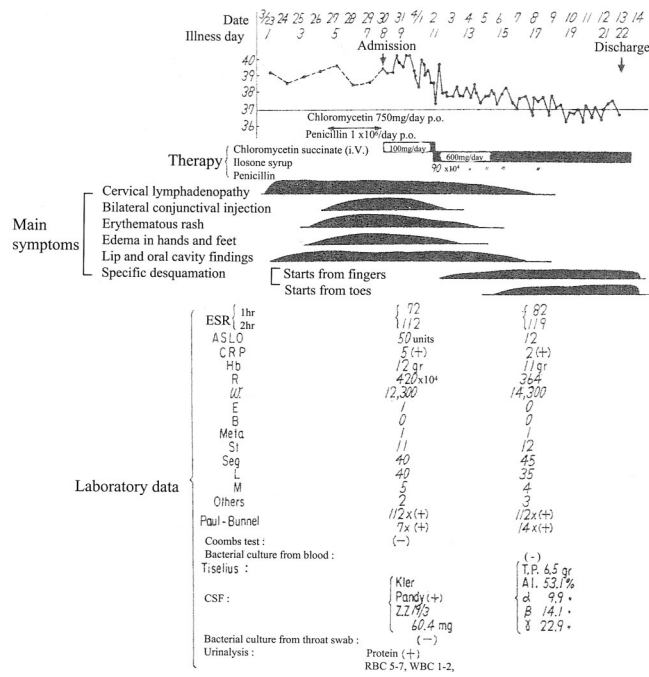
April 13: He still had bilateral desquamation of the hands and feet. However, he had completely recovered and was discharged.

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.

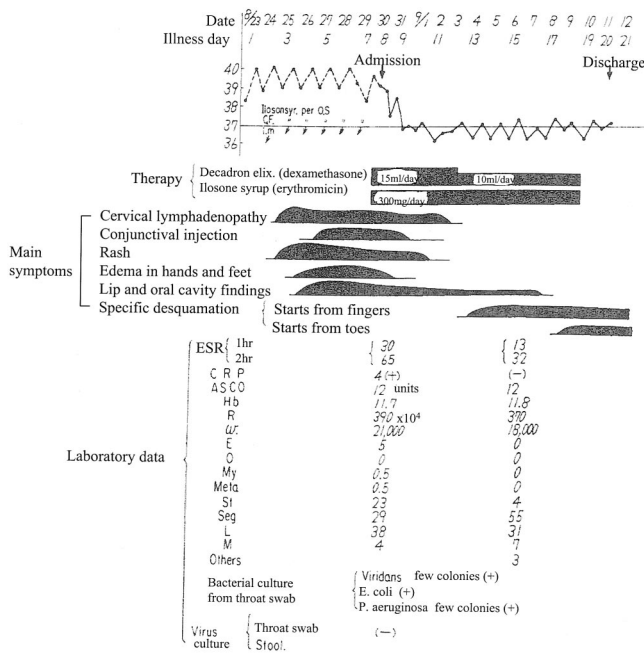
Discharged. September 11, 1965.

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.

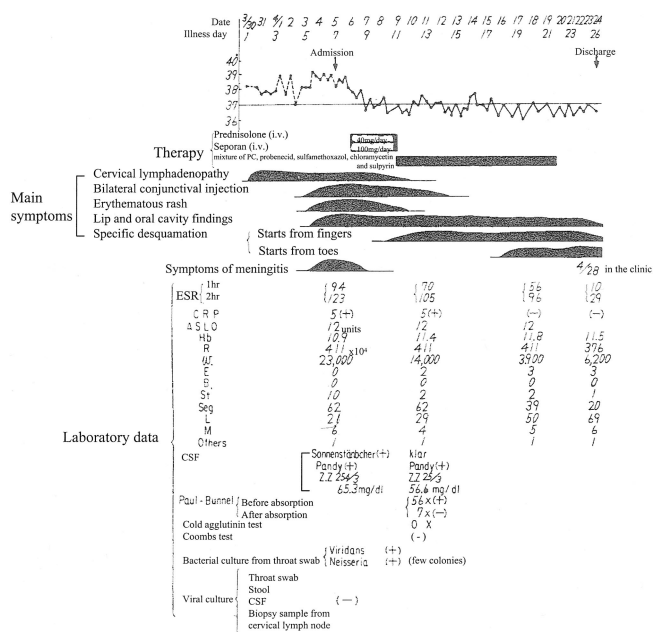
April 5: He had a fever of 39.5°C in the morning. He developed a new macular erythema on his chest and back. He had severe headache. The primary doctor referred him to the pediatric department in Japan Red Cross Hospital.

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.

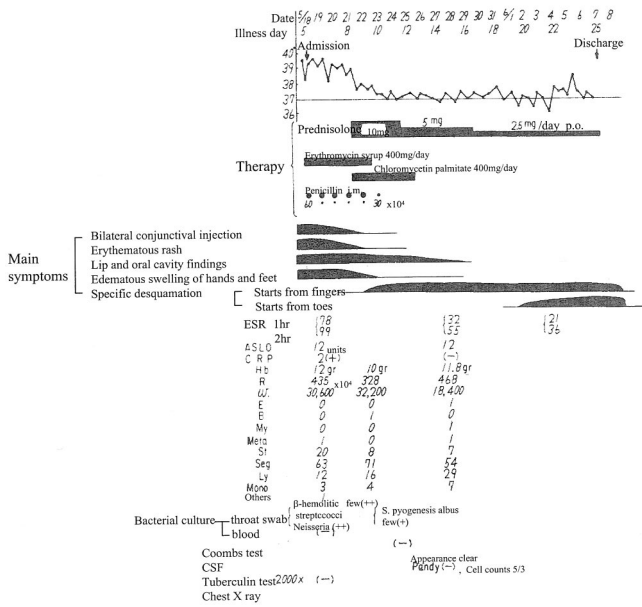
May 23: Desquamation started from between the nail and the exposed skin at the tip of the right thumb (Illness Day 11).

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.

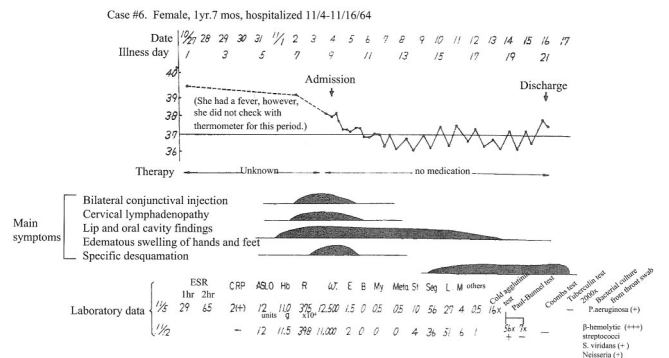
Discharged. September 6, 1966.

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.

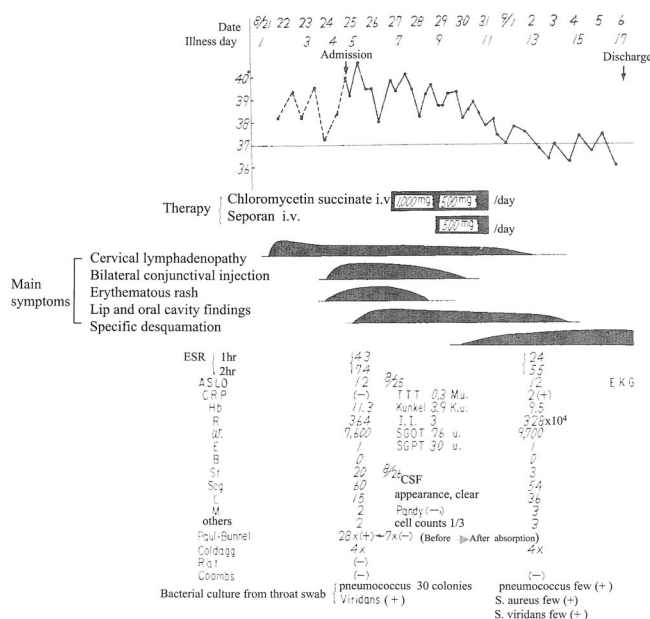
August 25: She had a fever of 40°C. She either cried unhappily or slept. She had mouth pain. She had erythema not only on her hands and feet but also on her body. Her primary doctor referred her to our department.

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	Kitazawa	Iruma-City	Nakano	Taito	Nerima		Shinjyuku	Bunkyo	Toshima	Kawaguchi	Musashino	Warabi	Machida	Fuchuu	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	1	16
Total	10	7	4	3	3	2	2	2	2	1	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

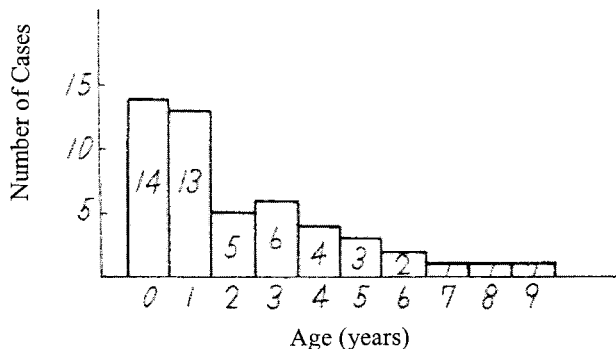
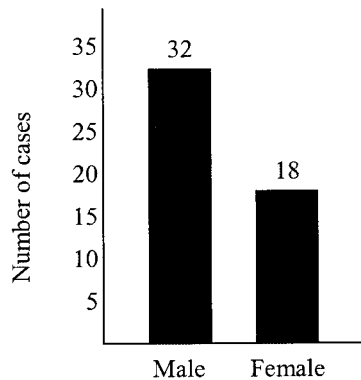
Table 3. Incidence by year and season.

	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.

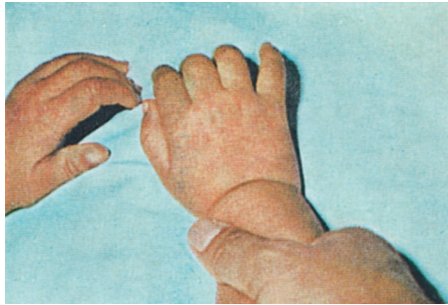


PHOTOGRAPH 19. Case 26. Congestion of bulbar conjunctiva (right side only) and catarrhal change of nares.



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.

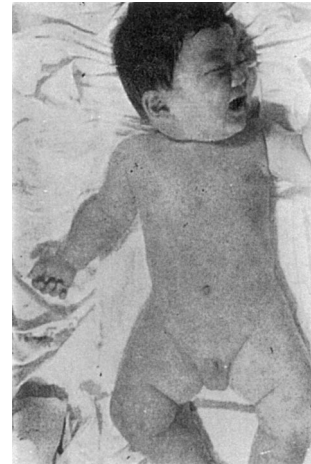


PHOTOGRAPH 11. Case 15. Rash on the nape of the neck and back.

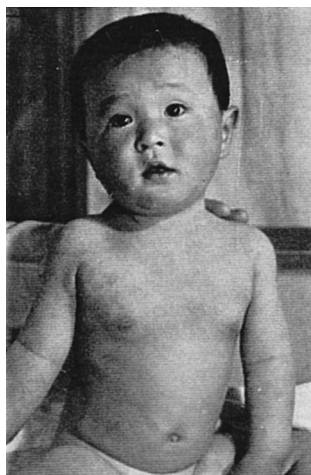
photographs, hands, feet and especially all the fingers and toes, palms and soles, and dorsa of the hands and feet swell so much that the skin becomes taut and shiny. This edema is nonpitting and was observed in 22 of 50 cases (44%). The finding was most common among the younger patients with 17 of 22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

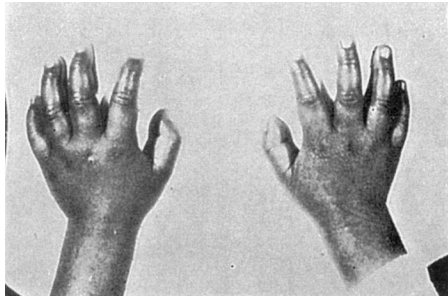
Illness Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total
No. of cases	4	2	3	2	6	9	6	1	4	1	1	0	1	0	40

Table 23. Order of appearance of rash

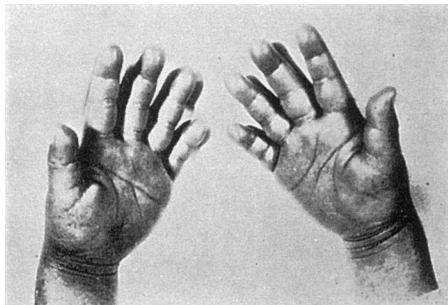
Appeared on extremities, especially palms and soles	29 cases (58%)
Appeared on chest, abdomen, back, face, or neck	14 cases (28%)
No rash (or not recognized)	7 cases (14%)

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.

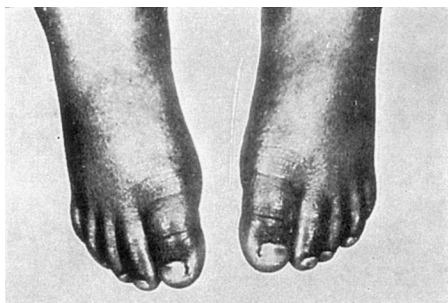
These lip and oral cavity findings were recognized in virtually all cases (48 of 50, 97%). It is possible that



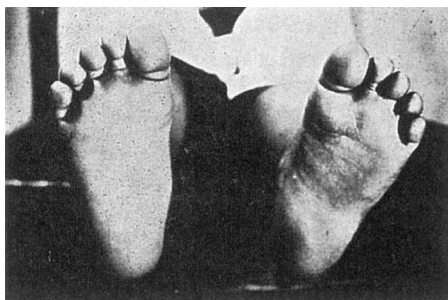
PHOTOGRAPH 22. Case 22. Vasoneurogenic, edematous swelling of the dorsa of both hands and all fingers.



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.

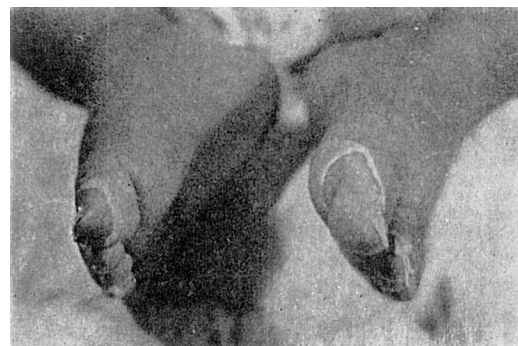
The pattern of desquamation on the toes and feet are almost same, but there were cases who presented with



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,

hands and feet, never extending across the wrist joint. Especially when the peeling is limited only to finger tips, it is easy to miss the finding. We had to observe very carefully even after the disappearance of fever. If we find skin peeling of this pattern, we can diagnose the case retrospectively by asking about the main symptoms as described before.

Those seven main symptoms are all important findings in this syndrome, and Tables 26 to 28 depict the relationship between the starting timings of each symptom. Generally CLA, rash, mouth changes, edema and fever had presented by Illness Day 7. These signs sometimes presented together, but sometimes the timing and order of presentation was different. Most of the time, peeling presented in the second week of illness (7th to 14th illness day), so it is clearly a later sign than the others. Thus I would say that peeling is a sign of the convalescent phase, and the other symptoms are of the acute phase.

8. Cases with unusual symptoms or findings.

Here I present the atypical symptoms or findings.

a. Cases with icterus (four cases, Table 29). The table shows the course of the laboratory data describing icterus and liver function (Cases 24, 33, 23 and 21). Icterus is not severe and resolves relatively quickly. Liver function is impaired only slightly.

b. Cases with nonbacterial meningitis (five cases, Table 30). The table shows the laboratory data regarding cerebrospinal fluid (Cases 1, 5, 7, 25 and 26). Although Case 5 presented with only a mild increase in cell count, he had meningitis symptoms clinically and I included him in the case study of this section. This case

Table 27. The order of symptoms in each case (Case#18-33)

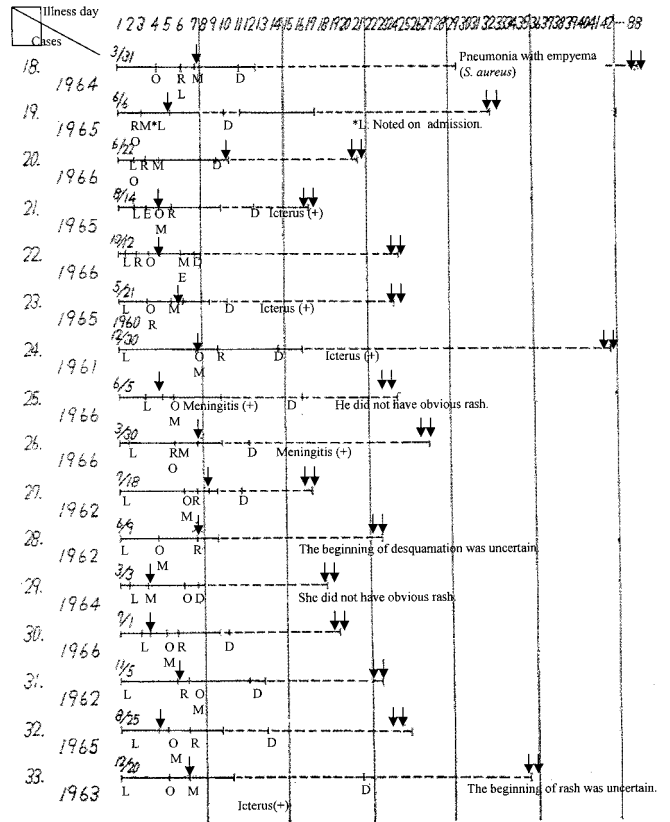
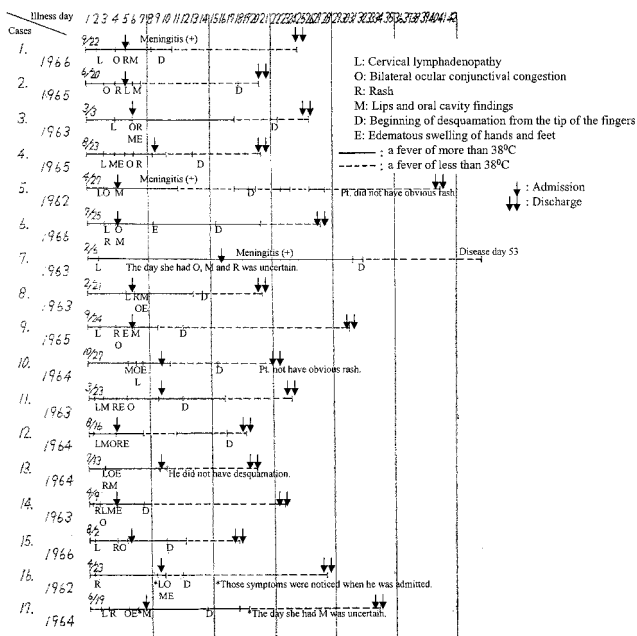


Table 26. The order of symptoms in each case (Case#1-17)



and the other four cases recovered from symptoms of meningitis relatively quickly.

All nine cases with either icterus or meningitis belong to the CLA+ group. The fact that there were no cases in CLA- group may suggest some pathologic difference between the CLA+ and CLA- groups.

c. Cases with acute otitis media. The Chief of Otorhinolaryngology at our hospital, Dr. Ogura, summarized the 13 cases examined by otorhinolaryngologists at our hospital. Seven cases were diagnosed with acute otitis media. All seven patients had bilaterally injected tympanic membranes without pus, even on incision. No cases developed suppurative otitis.

d. Cases with complaint of arthralgia (seven cases). The cases with complaint of arthralgia were Cases 19, 21, 17, 28, 49, 48 and 30. All were older than 2 years. None were diagnosed with frank arthritis by orthopedic examination or radiographic examination of the joint. Since all of them complained of arthralgia during fever, the consultant orthopedist said, "Probably, the arthralgia is brought on by fever." Since this syndrome is a generalized acute febrile disease as described before, it is natural to think that transient inflammation occurs in the joints as well as in other body sites. The relationship between the presence of arthralgia and the ASLO values is shown in Table 31. In five of seven cases the ASLO was slightly higher than 12 U,

Table 29. Course of icterus index and liver function in 4 cases with icterus

Case #	Age	Sex	Illness Day	Icterus index	Total bilirubin	Direct bilirubin	Ind bilirubin	TAKATA	TTI (Mu)	CCF	Gros	SGOT	SGOP	Kunkel (k.u.)
24	4y3m	m	13	20.0	2.6	1.5	1.1	-	2.8	+/-	+/-			
			17	26.7	4.8	2.6	2.2	-	4.0	-	+			
			19	20.0	2.8	1.2	1.6	+/-	3.15	+	+/-			
			27	11.0	1.0	0.3	0.7	-	2.7	+/-	+/-			
			33	11.4	1.2	0.4	0.8	-	2.5	-	-			
33	9y1m	m	38	8.0				-	2.0	-	-			
			7	60	8.1	4.7	3.4		1.2	++		54	68	8.4
23	4y2m	f	22	15	1.3	0.3	1.0							
			8	55	6.0	5.6	0.4		2.0			49		3.0
			11	15	1.3	1.2	0.1							
			15	8	0.8	0.6	0.2		3.0			19		5.0
21	3y9m	f	22	7	0.6	0.2	0.4							
			5	22						1.0				
			7	25							64	80	4.0	

Table 30. Findings in the cerebrospinal fluid in 5 cases with aseptic meningitis

Case #	Age	Sex	Illness Day	Pandy test	Nonne-Apelt	Cell Number WBC/3HPF	Glucose mg/dl
5	8m	m	5	+	+	42	59.2
			7	+/-		43	80.3
7	1y	f	17	++	+	495	47.8
			21	+		74	68.7
			41	+		38	66.1
26	5y1m	m	7	+		254	65.3
			13	+		25	56.6
25	4y7m	m	6	++	+	338	37.4
			9	+	+	34	69.6
			13	+	+	34	52.2
1	4m	m	5	+		248	
			8	+		82	59.2
			22	+		24	

Table 32. ESR of 1 hour (at hospitalization and maximum) and number of cases

ESR (mm)	No. of cases	
	At hospitalization	Maximum value
10-20	3	3
20-30	6	5
30-40	5	5
40-50	4	2
50-60	7	7
60-70	4	4
70-80	6	5
80-90	6	7
90-100	5	5
100-110	2	4
110-120	1	2
120-130	0	0
130-140	0	0
140-150	0	0
> 150	1	1
Total	50	50

Table 31. Relationship between arthralgia, pharyngeal bacterial isolation, and ASLO

Case #	Age	Arthralgia	Pharyngeal bacterial isolation	ASLO	Illness Day of ASLO
19	3y6m	+	β strep, pseudomonas, Neisseria, Staph. aureus	12	5
				12	16
				12	23
28	5y10m	+	β strep, Neisseria, α strep	333	8
				250	18
49	2y7m	+	Neisseria	2500	12
				2500	17
27	5y8m	+	α strep, Neisseria	50	9
				100	3
21	3y9m	+	Staph. epidermidis	100	9
				100	16
				12	17
48	2y3m	+	Neisseria, pseudomonas	50	4
				166	11
				125	18
30	6y9m	+	Neisseria, pseudomonas, Staph. aureus, β strep	50	61
				50	6
				100	12
36	6m	-	pseudomonas, Staph. aureus	100	6
				12	12
33	9y1m	-	pseudomonas	333	7
				625	29
32	8y7m	-	Neisseria	100	4
				125	20
29	6y4m	-	Neisseria, pseudomonas	1250	4
				2500	17
11	1y8m	-	β strep, α strep, Neisseria	50	10
				12	17
				125	28
1	4m	-	pseudomonas, Neisseria	50	6
				12	22
20	3y7m	-	-	100	10
				50	17
22	4y1m	-	-	50	6
				166	13
				100	24

Among them 4 cases (Cases 49, 29, 28 and 33) had titers of >250 Todd U. Two of them (Cases 29 and 33) had an increasing ASLO titer on the second test. Cases 50, 32, 11, 22 and 30 also presented with a low ASLO titer that increased on the second test. Therefore I described the relationship between the 7 cases with

Table 33. CRP (maximum value) and number of cases

CRP	0	1+	2+	3+	4+	5+	6+	7+	8+	9+	10+	Total
No. of cases	2	0	6	10	8	10	4	5	1	1	1	48

arthralgia and the 14 cases with an ASLO titer higher than 12 U and bacterial isolation from their throat in Table 31. Arthralgia, isolation of *Streptococcus* from the pharynx and ASLO titer did not show any correlation. Therefore I would say that there is not much relationship between this syndrome and *Streptococcus*, except in a few cases.

4. Isolation of bacteria from the pharynx (42 cases, Table 36). The most frequent isolates were *Neisseria* sp. and *S. viridans*, followed by alpha-hemolytic *Streptococcus*, *Staphylococcus aureus* and alpha-hemolytic *Streptococcus*. Therefore *Streptococcus* was not particularly significant.

5. White blood cell count (WBC) (50 cases, Table 37). A tendency toward leukocytosis was observed. This tendency was especially strong among older children, as 13 of 23 cases >2 years old (56.5%) had a WBC >15 000/mm³, compared with only 8 of 27 (30%) in cases <2 years old .

6. Left shift of WBC (50 cases, Table 38). Various degrees of left shift of the WBC were observed in 41 of 50 cases (82%).

7. Change in eosinophil count (50 cases, Table 39). The eosinophil count at the time of hospitalization was

Table 34. Relationship between change of CRP and ESR (1 hour value)

Case #	Illness Day	CRP	ESR	Use of steroids	Case #	Illness Day	CRP	ESR	Use of steroids
25	4	8+	61	-	28	8	-	75	-
	20	-	33	-		16	-	15	-
16	8	5+	96	-	45	6	2+	58	-
	23	-	12	-		11	-	21	-
47	6	4+	112	-	46	7	3+	52	-
	18	-	70	-		23	-	13	-
42	6	2+	78	+	8	7	5+	86	-
	15	-	32	-		19	-	26	-
5	6	6+	36	+	7	17	5+	98	+
	23	-	20	-		41	-	20	-
3	7	2+	40	+	14	4	2+	73	-
	21	-	15	-		14	-	18	-
29	4	10+	107	-	13	9	-	11	-
	17	-	64	-		15	-	8	-
18	7	7+	58	-	17	8	5+	86	+
	17	-	23	-		25	-	17	-
50	6	3+	36	+	10	10	2+	29	-
	12	-	29	-		17	-	8	-
49	12	4+	108	+	23	11	3+	11	+
	17	-	27	-		22	-	14	-
19	5	3+	53	+	2	9	3+	84	+
	23	-	19	-		20	-	9	-
40	6	4+	25	+	21	3	3+	25	+
	17	-	18	-		16	-	16	-
32	4	4+	61	+	4	8	4+	30	+
	14	-	41	-		15	-	13	-
33	7	5+	38	-	26	7	5+	94	+
	20	-	17	-		20	-	56	-
36	6	4+	35	-	1	6	6+	-	-
	20	-	10	-		22	-	18	-
6	4	9+	81	-	15	10	7+	85	-
	25	-	25	-		17	-	20	-
22	6	6+	64	-	38	7	6+	72	-
	24	-	10	-		18	-	27	-
44	5	4+	63	-	30	4	7+	58	+
	20	-	9	-		61	-	9	-

Table 35. ASLO value (>12 U), 14 cases

Case #	Age	Illness Day	ASLO (units)	Case #	Age	Illness Day	ASLO (units)	Case #	Age	Illness Day	ASLO (units)		
49	2y7m	12	2,500	22	4y1m	6	50	21	3y9m	3	100		
		17	2,500			13	166			9	100		
29	6y4m	4	1,250	1	4m	24	100	36	6m	16	100		
		10	2,500			6	50			6	100		
		17	2,500			22	12			12	12		
33	9y1m	7	333	27	5y8m	9	50	30	6y9m	4	50		
		20	625			32	8y7m			14	100	11	166
		29	625							4	100	18	125
28	5y10m	8	333	11	1y8m	20	125	20	3y7m	61	50		
		18	250			10	50			10	100		
50	3y4m	6	50	28	125	17	12	20	3y7m	17	50		
		12	166			28	125						

ASLO tested ≥ 2 times 44 cases ASLO 12 U at least twice 31 cases
 ASLO tested once 5 cases ASLO 12 U tested once 4 cases
 ASLO not tested 1 case

Table 36. Bacterial isolates from pharynx (42 cases)

Bacterial isolates	No. of cases
<i>Neisseria sp.</i>	26
<i>Streptococcus viridans</i>	23
α-hemolytic streptococcus	11
<i>S. aureus</i>	11
β-hemolytic streptococcus	7
<i>Staphylococcus epidermidis</i>	6
<i>Esherichia coli</i>	3
<i>Klebsiella sp.</i>	2
<i>Candida albicans</i>	2
<i>Bacillus pyocyaneus</i>	1
<i>Streptococcus pneumoniae</i>	1

generally decreased. I did not see a case with an increased eosinophil count.

8. Change in monocyte count (50 cases, Table 40). Monocyte counts were usually normal or slightly increased.

9. Change in lymphocyte count (50 cases, Table 41).

Table 37. Relationship between white blood cell count (at hospitalization) and age

WBC count /mm ³	No. of cases in each age group									Total	
	0y	1y	2y	3y	4y	5y	6y	7y	8y		9y
< 5,000	5	2	1	0	0	1	0	0	0	0	9
5,000-10,000	4	8	1	2	1	1	1	1	1	0	20
10,000-15,000	3	0	1	1	1	0	1	0	0	0	7
15,000-20,000	2	1	2	2	1	1	0	0	0	0	9
20,000-25,000	0	0	0	1	0	0	0	0	0	0	1
25,000-30,000	0	1	0	0	1	0	0	0	0	1	3
30,000-40,000	0	1	0	0	0	0	0	0	0	0	1
Total	14	13	5	6	4	3	2	1	1	1	50

Table 38. Left shift of white blood cells

Type of WBC	No. of cases
Pre-myelocyte	2
Myelocyte	13
Post-myelocyte	13
Band more than 10%	13
Total	41

Table 39. Eosinophil count

Eosinophils (%)	No. of cases	
	At hospitalization	Maximum
0	19	6
0.5	3	3
1	12	11
1.5	1	0
2	6	12
3	4	7
4	2	4
5	3	5
8	0	1
10	0	1
Total	50	50

Table 40. Monocyte count (%)

Monocytes (%)	No. of cases	
	At hospitalization	Maximum
1	7	0
2	9	2
2.5	1	0
3	9	8
4	7	8
5	6	7
6	7	12
7	3	7
8	0	5
23	1	1
Total	50	50

Table 41. Lymphocyte (%) on admission and (maximum data)

%	Age (yrs.)									Total		
	0	1	2	3	4	5	6	7	8		9	
0		1			1	2				1	1	6 (0)
10		1	3	3	1		2	1 (1)				11 (1)
20	6	5 (1)	1 (2)	2 (1)		1						15 (4)
30	4 (1)	2 (2)	1 (1)	(2)	1 (2)	2 (1)		(1)				10 (10)
40	1 (3)	2 (3)	(2)		(1)							3 (9)
50	1 (5)	1 (1)		(2)	(1)	(1)	(2)			(1)		2 (13)
60	1 (3)	1 (6)			(1)							2 (10)
70				(1)								0 (1)
80	1 (2)											1 (2)
Total	14	13	5	6	4	3	2	1	1	1	1	50 (50)

Generally the lymphocyte count was low at the time of hospitalization but recovered in convalescence. The table shows the percent lymphocytes by age group at the time of admission and at the peak.

10. Coombs test (35 cases). A Coombs test were performed on 35 cases. Only Case 24 had a direct positive Coombs [reaction]. All the other cases were negative.

Table 42. Paul-Bunnell results (agglutinin value by Kumagaya modification) 0.5% goat hemocytes were used.

		7x		14x		28x		56x		112x		224x		448x		Total
		-	+	-	+	-	+	-	+	-	+	-	+			
Absorption on guinea pig kidney	Before	1	1	2	10	18	3	0	1*	0	0	0	0	0	0	36
	After	27	7	0	1	0	1*	0	0	0	0	0	0	0	0	36

*Positive case

11. Paul-Bunnell reaction (36 cases, Table 42). Case 27 had a hemagglutination titer of 1:448 before absorption onto guinea pig kidney cells and a titer of 1:112 after absorption, thus interpreted as positive. The other 35 cases were negative.

12. Cold agglutination reaction (24 cases). All were <1:16, which indicates a negative cold agglutination reaction.

13. Blood culture (12 cases). All cultures were negative, although we have to consider that most of the cases were being treated with antibiotics at the time of the culture.

14. Urinalysis (39 cases). Proteinuria was detected at the time of hospitalization in 22 of 39 cases (56.4%) and was probably febrile proteinuria. In no case was pyelonephritis or nephritis suspected based on the urinary sediment.

15. Tiselius (20 cases, Table 43 [in which T.P. is total protein, Alb. is albumin and Gl. is globulin]). Six cases (30%) had an elevated gamma-globulin fraction (over 22%).

16. Rheumatoid factor (10 cases, Table 44). Three cases (Cases 21, 22 and 30) had a positive or mildly positive rheumatoid factor [RF]. Table 44 depicts the results of the rheumatoid factor and its relationship to the CRP and ASLO.

17. LE [lupus erythematosus] phenomenon (4 cases, Table 45). Four cases (Cases 30, 22, 43 and 6) were tested for LE cells and were negative.

18. Serum ALT and AST (14 cases, Table 46). Three cases (Cases 21, 33 and 23) presented with icterus as described above. However, we recognized either mild, transient elevations of both serum ALT and AST or only serum ALT even in cases without icterus in the early stage of disease or later in the course (Cases 25 and 38).

Table 43. Tiselius (20 cases)

T.P.	4.5-5.0	5.1-5.5	5.6-6.0	6.1-6.5	6.6-7.0											Total
	1	6	3	6	4											20 cases
Alb.	30-39	40-49	50-59	60-69	70-79											Total
	0	2	14	4	0											20 cases
α-Gl.	7.0-7.9	8.0-8.9	9.0-9.9	10.0-10.9	11.0-11.9	13.0-13.9	15.0-15.9	16.0-16.9	21.0-21.9							Total
	1	2	3	5	3	1	2	2	1							20 cases
β-Gl.	8.0-8.9	9.0-9.9	10.0-10.9	11.0-11.9	12.0-12.9	13.0-13.9	14.0-14.9	15.0-15.9	16.0-16.9							Total
	1	1	5	0	6	1	4	0	2							20 cases
γ-Gl.	13.0-13.9	16.0-16.9	17.0-17.9	18.0-18.9	19.0-19.9	20.0-20.9	21.0-21.9	22.0-22.9	24.0-24.9	26.0-26.9	29.0-29.9					Total
	1	1	1	2	2	3	4	2	1	2	1					20 cases

Table 44. RF test, CRP, ASLO (10 cases)

Case #	Illness day	RF	CRP	ASLO
21	16	Slight positive	-	100 units
22	6	Slight positive	6+	50
	13	-	1+	166
30	18	Positive	4+	125
	61	Positive	-	50
19	16	-	4+	12
26	20	-	-	12
1	6	-	6+	50
15	5	-	-	12
44	5	-	4+	12
39	12	-	1+	12
48	17	-	5+	12

Table 45. LE cell examination (4 cases)

Case #	Illness day	LE cells
40	7	(-)
22	15	(-)
43	15	(-)
6	10	(-)

Table 46. Icteric index, SGOT, and SGPT (14 cases)

Case #	Illness day	Icteric index	SGOT	SGPT	Note
21	6	25	64	80	Icteric case
33	7	60	54	68	Icteric case
23	8	55	49	-	Icteric case
25	5	8	19	-	Meningitis case
	7	2	33	19	
	10	1	65	40	
	13	-	83	59	
	17	1	39	39	
	20	3	31	-	
9	14	3	29	-	
1	6	1	52	44	Meningitis case
6	8	2	37	39	
15	5	3	76	30	
22	6	3	26	24	
38	7	3	33	18	
	14	-	56	31	
43	5	5	138	141	
	10	-	37	33	
44	5	2	37	18	
30	7	7	84	166	
	11	5	37	44	

19. ECG (12 cases, Table 47). Case 15 had a prolonged PQ. The patient was observed without using steroids and was confirmed to recover completely 3 months later, December 8, 1966. The heart sounds remained normal during the entire disease course. The other 11 cases tested did not show any abnormality.

20. Relationship between BCG [bacillus of Calmette-Guérin] inoculation and this syndrome (Table 48). In the medical records, I found 19 cases inoculated with BCG before the episode of this syndrome. The date of the inoculation was obtained in 16 cases. No strong relationship between this syndrome and inoculation

Table 47. EKG (12 cases)

Case #	Illness day	Date	EKG No.	Findings
36	20	1.24.66	No. 197	Tachycardia
26	21	4.19.66	No. 1075	normal
32	20	9.13.65	No. 2103	normal
21	9	8.23.65	No. 1917	normal
33	24	1.11.64	No. 54	Tachycardia
30	16	7.16.66	No. 2118	Respiratory arrhythmia
15	17	9.6.66	No. 2566	Prolonged PQ
44	9	10.8.66	No. 2884	normal
22	15	10.26.66	No. 3072	Respiratory arrhythmia
20	20	7.16.66	No. 2122	normal
48	18	8.13.66	No. 2369	Tachycardia
6	20	8.13.66	No. 2376	Tachycardia

Table 48. The relationship between B.C.G. inoculation and disease onset

No. of cases	Interval between B.C.G. inoculation and disease onset											Inoculation date is not clear	Inoculation is not clear	No inoculation	Total		
	1 m.	2	3	5	6	7	9	10	11	1y 6m	2y					4y	
	1	1	1	1	2	2	1	1	1	1	1	3	1	3	14	17	50

with BCG was suggested. The relationship to other immunizations cannot be discussed here, because the date of the inoculations is not precisely available in most of the cases.

21. *Virus isolation and serology (Tables 49 to 51).* Dr. Ashihara at the National Institute of Infectious Disease kindly performed viral isolation from the pharynx, nasal swab, CSF and stool in 14 cases and from the cervical lymph node in Case 26. Thus far no virus has been isolated from any sample (Table 49).

In some cases complement fixation titers were performed for Coxsackievirus A16, echovirus 11 and adenovirus 3. But, as shown in Table 50, Coxsackievirus A16 and echovirus 11 were both negative. An increased serum antibody titer against adenovirus 3 in the convalescence compared with the acute phase was observed in two cases, Cases 26 and 23. The results from Cases 9 and 39 suggested an antecedent adenoviral infection.

Since more attention has been paid to the relationship between PPLO [pleuropneumonia-like organisms] and MCOS recently, Dr. Nakamura at the Institute of Infectious Disease, University of Tokyo, kindly tested the complement fixation titer against PPLO in five cases.^(9,10) All cases were negative, as shown in Table 51. From among these results, especially from some of the serologic results, it is worth pursuing the relationship between this syndrome and adenoviral infection.

22. *Histologic examination of the skin (7 cases, Table 52 and Photographs S-1 to S-12).* As I previously explained, clinical features in the skin are important findings in this syndrome. In particular I wondered whether there might be any specific change at the junction of skin and nail on the tip of the fingers and toes. Thus I compared biopsies of these regions with

Table 49. Virus culture (by Dr. Ashihara in the National Institute of Infectious Disease 1965-1966)

Case #	Sample collection date		Sample	Hela	MK	HEL	SM
	Illness day	Date					
2	6	5/26	K, T, N	-	-	-	-
4	12	6/7	K, T, N	-	-	-	-
9	12	3/4	K, T	-	-	-	-
19	5	6/10	K, T	-	-	-	-
21	6	6/25	K, T	-	-	-	-
23	6	7/10	K, T	-	-	-	-
26	3	3/28	K	-	-	-	-
32	7	1/11	K	-	-	-	-
36	7	3/18	K	-	-	-	-
39	8	10/1	K, T	-	-	-	-
40	8	8/30	K	-	-	-	-
41	7	8/20	K, T	-	-	-	-
26	7	4/5	K, L	-	-	-	-
32	6	8/30	K	-	-	-	-

K: stool, T: throat swab, N: nasal swab, L: lymph node, -: CPE negative

Table 50. Complement-fixation reaction for Cox A 16, ECHO11, and Adeno 3 (by Dr. Ashihara in the National Institute of Infectious Disease)

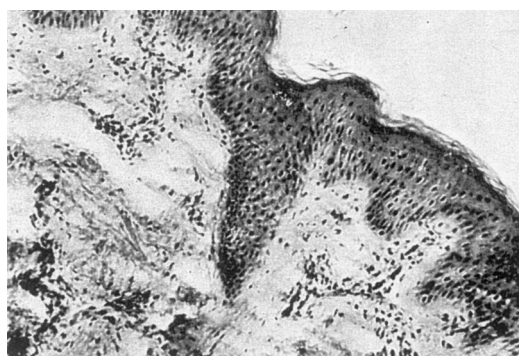
Case #	Serum collection date	Illness day	CoxA-16	Echo11	Adeno 3
36	1.1.66	7	<1:4	<1:4	<1:4
	1.24.66	20	<1:4	<1:4	<1:4
9	10.1.65	8	<1:4	<1:4	1:64
	10.20.65	27	<1:4	<1:4	1:32
26	4.4.66	7	<1:4	<1:4	<1:4
	4.22.66	24	<1:4	<1:4	1:16
39	3.28.66	3	<1:4	<1:4	1:16
	4.11.66	17	<1:4	<1:4	1:16
23	5.26.65	6			<1:4
	6.23.65	34			1:8
35	6.7.65	12			<1:4
	6.25.65	30			<1:4
19	6.6.65	5			<1:4
	7.7.65	35			<1:4
2	6.25.65	6			<1:4
	7.7.65	18			<1:4
40	7.10.65	6			<1:4
	8.3.65	30			<1:4

Table 51. Complement-fixation reaction for PPLO (Dr. Nakamura in the Institute of Infectious Disease, University of Tokyo)

Case #	Serum	I.V.B.S.	I.N.A.	Serum dilution				Results
				1:4	1:8	1:16	1:32	
23	Acute	0	0	0+	0	0	0	?
	Convalescent	0	0+	3	0+	0	0	
35	Acute	0	0	0	0	0	0	Negative
	Convalescent	0	0	0	0	0	0	
19	Acute	0	0	0	0	0	0	Negative
	Convalescent	0	0	0	0	0	0	
2	Acute	0	0	0	0	0	0	Negative
	Convalescent	0	0	0	0	0	0	
9	Acute	0	0	0	0	0	0	Negative
	Convalescent	0	0	0+	0+	0	0	
Control serum from PPLO patient	Convalescent	0	0	4	4	4	3	Positive

Table 52. Histological examination of skin (7 cases)

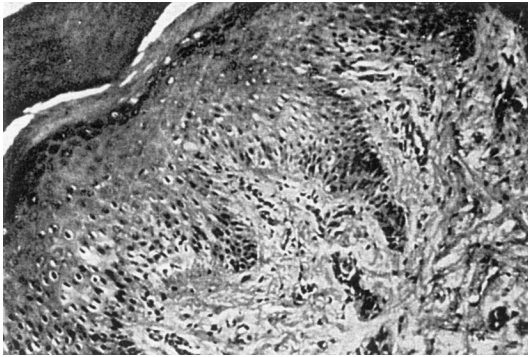
Case #	Age	Biopsy date	Illness day	Biopsy area	Pathology No.	Anesthesia
36	6m	1.12.66	8	Tip of right thumb, Middle of left thigh	No. 58060	-
41	1y	3.18.66	7	Tip of left thumb, Above left knee	No. 59998	-
39	9m	3.28.66	3	Tip of left first toe, Above right knee	No. 60261	-
26	5y1m	4.6.66	8	Lateral right foot	No. 60494	Local
30	6y9m	7.5.66	5	Tip of left second toe	No. 63058	Field
15	2y5m	8.26.66	6	Tip of right third toe, buttock	No. 64417	-
1	4m	9.27.66	7	Tip of right first toe, Above left knee	No. 65482	-



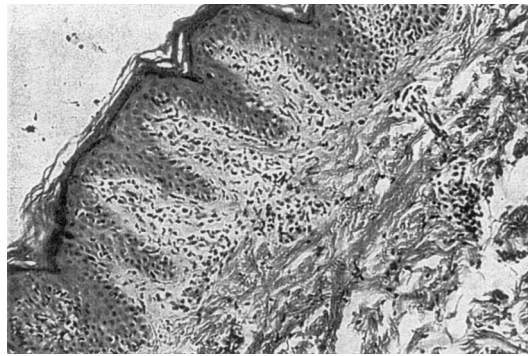
PHOTOGRAPH S-1. Case 36. Subepidermal edema and cellular infiltration around the capillary.

other areas of erythematous skin obtained at the same time (Cases 36, 41, 39, 15 and 1).

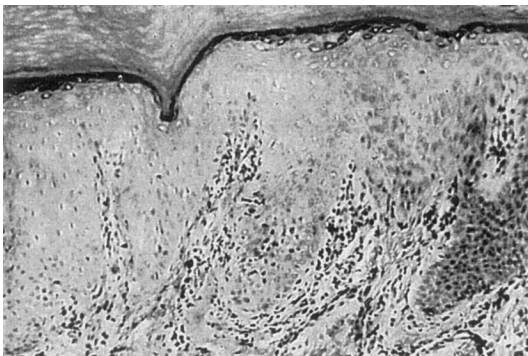
Case 26 was biopsied with local anesthesia. Cases 36, 41, 39, 15 and 1 were infants, and I wanted to obtain the histology without distortion, so they were biopsied without anesthesia. Case 30 was biopsied on



PHOTOGRAPH S-2. Case 36. Nail-skin junction: exfoliation of horny layer, subepidermal edema, slight infiltration of lymphocytes and white blood cells around the capillary.

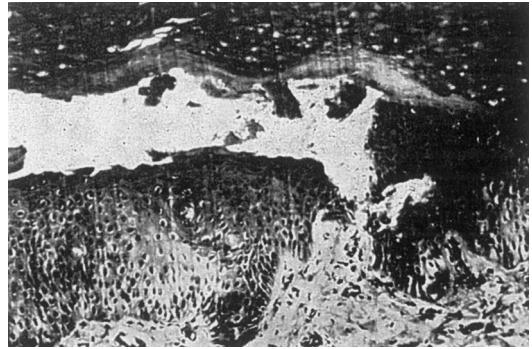


PHOTOGRAPH S-3. Case 41. Subepidermal edema and major cellular infiltration around the capillary.



PHOTOGRAPH S-4. Case 41. Nail-skin junction: marked cellular infiltration around the subepidermal capillary (lymphocytes, monocytes and white blood cells).

the toe following a nerve block because he was a school age child. The biopsy details of those 7 cases are shown in Table 52. The histologic features of each biopsy are shown in Photographs S-1 to S-12. According to Dr. Noboru Tanaka, the chief pathologist of our hospital, the common features of the histologic changes in the skin in this syndrome are: (a) the keratin layer peels at the tip of the fingers and toes where there is a thick keratin layer; (b) all the skin biopsies, including those of the tips of fingers and toes, show severe edema, dilatation of some capillaries and mild cell (especially lymphocytes and monocytes) infiltration around blood



PHOTOGRAPH S-5. Case 26. Exfoliation of the horny layer.



PHOTOGRAPH S-6. Case 39. Marked subepidermal edema, capillary dilatation and slight cellular infiltration around the capillary.



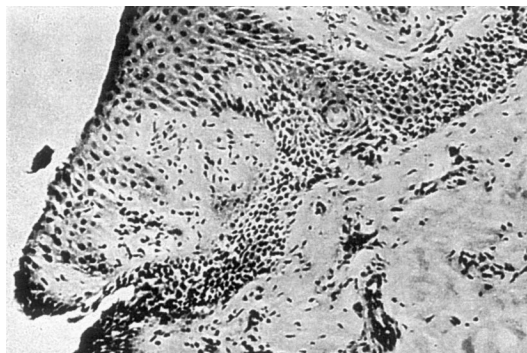
PHOTOGRAPH S-7. Case 30. Nail-skin junction. Exfoliation of the horny layer.

vessels in the connective tissue right under the dermis; (c) the change described in [Clause] b is generally similar to the findings in erythema.¹¹

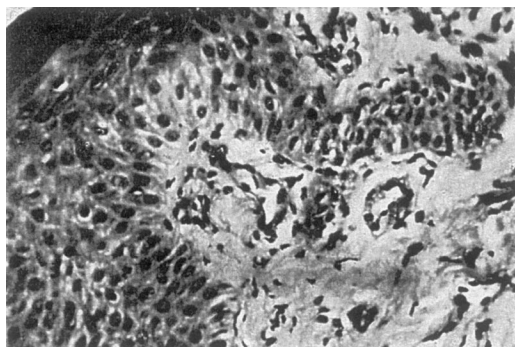
23. *Histologic examination of cervical lymph node* (3 cases, Table 53 and Photographs L-1 to L-6). I wondered whether there were any specific changes in the cervical lymph node because its swelling is a specific symptom of this syndrome. With the help of Dr. Huttonaka, Chief Surgeon, and Dr. Kajitani, both surgeons at our hospital, lymph nodectomy was performed in 3 cases (Table 53). Cases 26 and 6 still had cervical adenopathy bigger than the head of the thumb, but the biggest ones were under the sternocleidomastoid muscle and hard to extract. Therefore we removed the more



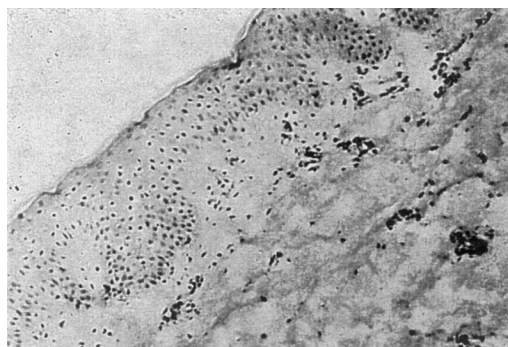
PHOTOGRAPH S-8. Case 30. Exfoliation of horny layer, subepidermal edema, mild cellular infiltration around the capillary.



PHOTOGRAPH S-10. Case 15. Complete exfoliation of the epidermal horny layer, subepidermal edema and mild cellular infiltration around the vessel.



PHOTOGRAPH S-9. Case 30. High magnification, subepidermal edema, dilatation and mild cellular infiltration around the capillary.



PHOTOGRAPH S-11. Case 15. Marked edema of the subcutaneous tissue, especially the subepidermal region.

superficial lymph nodes the size of a grain of rice. Case 1 fortunately had a big lymph node the size of the head of the thumb, which was located anterior to the sternocleidomastoid muscle and was relatively easy to extract. The histologic features are shown in Photographs L-1 to L-6. Dr. Tanaka pointed out the very specific pathologic changes, common to the 2 cases, that can be recognized in the higher magnification photographs, L-3 and L-6: (a) abnormal hyperplasia of the endothelium of the postcapillary venule; (b) hyperplasia of the reticular cells around the postcapillary venule. These may be important findings, a possible key to the etiology, and we will continue to study this in future.

TREATMENT

As described above, the natural course of this syndrome is benign, and I did not experience patients with either death or sequelae. The severity and symptoms varied in each case; some were very severe but others were almost entering the convalescent phase at the time of hospitalization. From the clinical symptoms and laboratory data, it is natural to suspect a general febrile disease caused by infection and to treat the patients with antibiotics, even though we do not know the etiology. For this reason all but 3 cases were treated with various antibiotics after hospitalization.

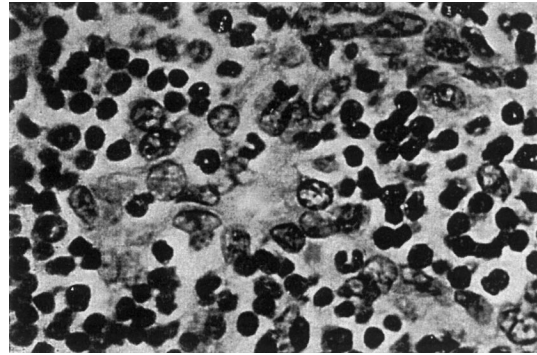
The other medication was steroids, which 22 cases received. According to the combination of the main treatment, we divided our 50 cases into 5 groups and compared them.

Group 1: no treatment after hospitalization (3 cases, Table 54). Cases 10, 13 and 22 were hospitalized on the ninth, ninth and fourth illness days, respectively. Case 22 was treated with chloromycetin succinate iv, 500 mg once a day for 2 days, and erythromycin syrup, 300 mg/day orally for 2 days, before hospitalization. I could not obtain precise information about the treatment before hospitalization in the other two cases, but since they had persistent fever of 38–40°C, there is no doubt that they had been treated with antibiotics. In spite of this we merely observed them with no intervention after hospitalization, and they recovered completely without any problem.

Group 2: treated with penicillin (8 cases, Table 55). Many cases were treated with more than two different kinds of antibiotics. Therefore I divided these cases into two groups based on penicillin usage. Eight cases were treated with penicillin and 17 cases were treated with antibiotics other than penicillin, as shown in the table. Among the 8 cases treated with penicillin, only Case 27 had penicillin from the early stage of the disease from an outpatient clinic. The other 7 cases were started on penicillin after hospitalization. As



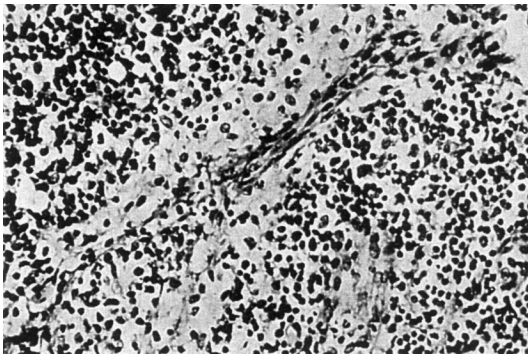
PHOTOGRAPH S-12. Case 1. Subepidermal blister formation, exfoliation of epidermis and marked subepidermal edema, mild cellular infiltration around the vessel.



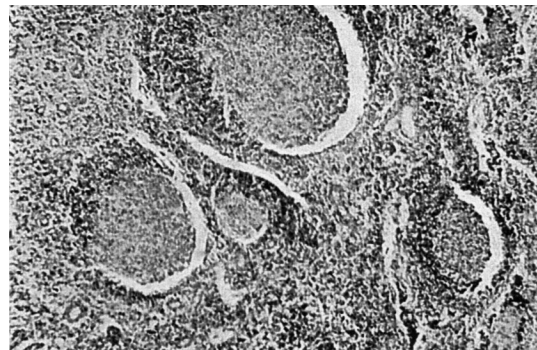
PHOTOGRAPH L-3. Case 6. High magnification, unusual swelling of endothelial cells in a postcapillary venule, proliferation of reticulum cells around that lesion.

Table 53. Histological examination cervical lymph node (3 cases)

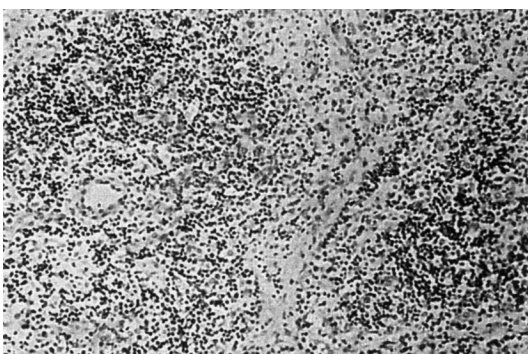
Case #	Age	Biopsy date	Illness day	Biopsy		Pathological No.
				Side	Size	
26	5y1m	4. 6.66	8	Right	Rice grain	No. 60459
6	11m	7.30.66	6	Right	Rice grain	No. 63726
1	4m	9.28.66	7	Left	Tip of a thumb	No. 65482



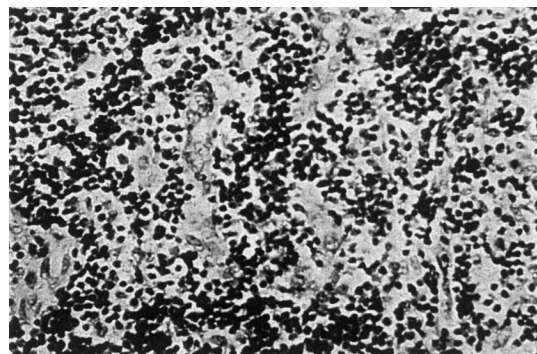
PHOTOGRAPH L-1. Case 26. Atypical chronic lymphadenitis accompanied by inflammation of the lymph node sinus with infiltration of white blood cells.



PHOTOGRAPH L-4. Case 1. Prominent development of lymph node secondary follicles.



PHOTOGRAPH L-2. Case 6. Lymph node sinus inflammation, proliferation of postcapillary venules without lymphoid follicle hyperplasia.

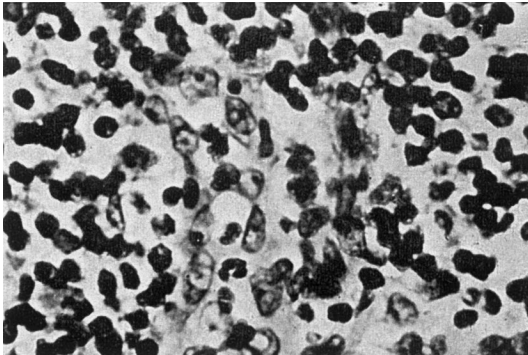


PHOTOGRAPH L-5. Case 1. Prominent development of postcapillary venules in medulla, marked swelling of endothelial cells.

shown by the fever curve in each case, no difference in effectiveness was observed when this group was compared with the other treatment groups.

Group 3: treated with antibiotics other than penicillin after hospitalization (17 cases, Tables 56.1 and 56.2). Cases 17 and 41 had clear information

from their referring doctors that they had been treated with injections of mycillin and penicillin, which were discontinued after hospitalization, so they were included in this group. As already described, Case 17 had a complication of pneumonia and case 18 had pneumonia and empyema caused by *Staphylococcus aureus* as a nosocomial infection. Those two cases plus Cases 15, 29, 33, 36, 39 and 41 were treated with intravenous chloromycin succinate as well as hydration. In addition to these medications, Cases 1, 38 and 43 were treated with intravenous sevoran, erythromycin or kitasamycin. Case 37 had only tetracycline HCl syrup orally, and 5 cases (Cases 6, 20, 44, 48 and 50) had only



PHOTOGRAPH L-6. Case 1. High magnification, swelling of endothelial cells of postcapillary venule, infiltration of inflammatory cells including white blood cells, proliferation of reticulum cells around that lesion.

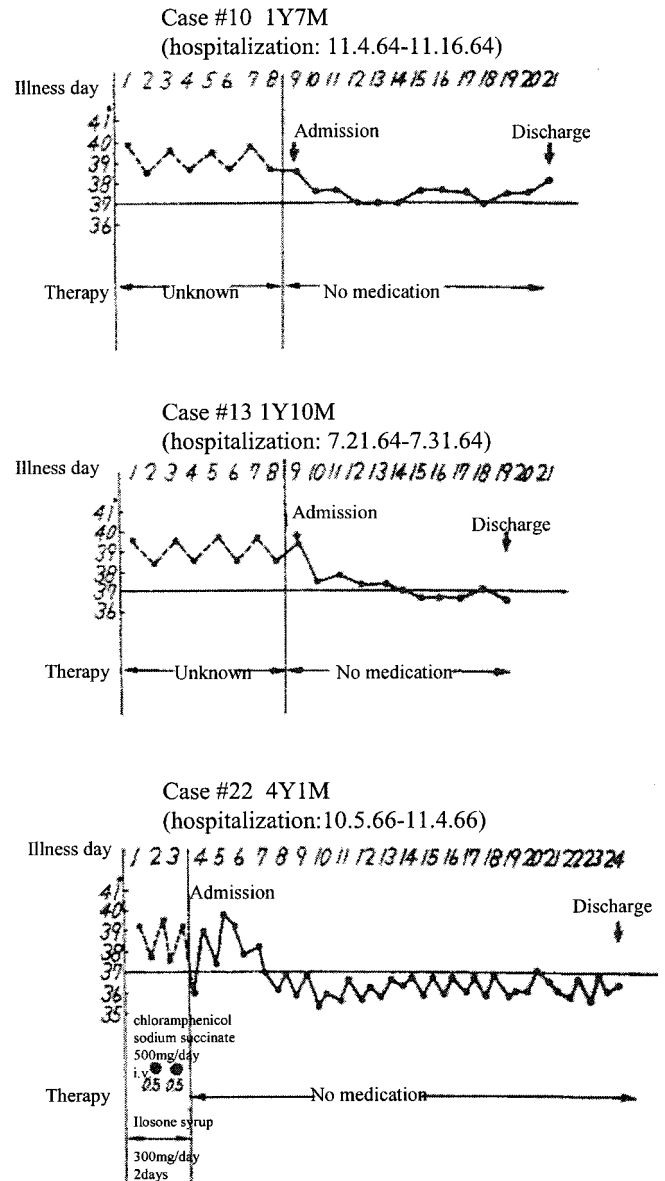
eythromycin syrup orally. This group fared neither better nor worse than did the other treatment groups.

Group 4: treated with steroids intravenously (8 cases) and intramuscularly (1 case) (Tables 57-1 and 57-2). Steroid hormone treatment was introduced by three routes: intravenously, intramuscularly and orally. Intramuscular injection of steroids was given only to Case 24, without any apparent effect. Eight cases (Cases 2, 19, 23, 25, 26, 30, 32 and 40) were treated intravenously with prednisolone 20 to 80 mg/day as well as with the other antibiotics and with hydration for 1 to 6 days. Among these patients fever appeared to respond to steroid therapy and disappeared in 5 cases (Cases 2, 19, 23, 30 and 40) but recurred with cessation of therapy. Clearly intravenous infusion of prednisolone was effective in terminating the fever and improving the general condition, but it is not clear that it helped to shorten the overall course of this syndrome, since we did not see a significant difference when compared with the other treatment groups. We need to be cautious in judging the effect of this therapy.

Group 5: Treated with steroids orally (13 cases, Tables 58-1 and 58-2). Three medicines, prednisolone, paramethasone acetate and dexamethasone, were used. Some cases were treated in the early phase of the disease, and others were treated in a much later phase, which makes it extremely difficult to judge their effectiveness. Except for Case 7 it seemed that oral steroids had some effectiveness in terminating fever transiently, even though it was not as dramatic as after intravenous administration. I could not find any more significant effect compared with the other treatment groups. It is difficult to judge the effectiveness of medication in a self-limited disease like this syndrome.

Tables 59-1 and 59-2 show the list of medications in each case and demonstrate that most cases received more than two medications. It is an interesting question whether this syndrome resolves away without any use of antibiotics. It is not possible to see cases who

Table 54. Cases observed during hospitalization without therapy

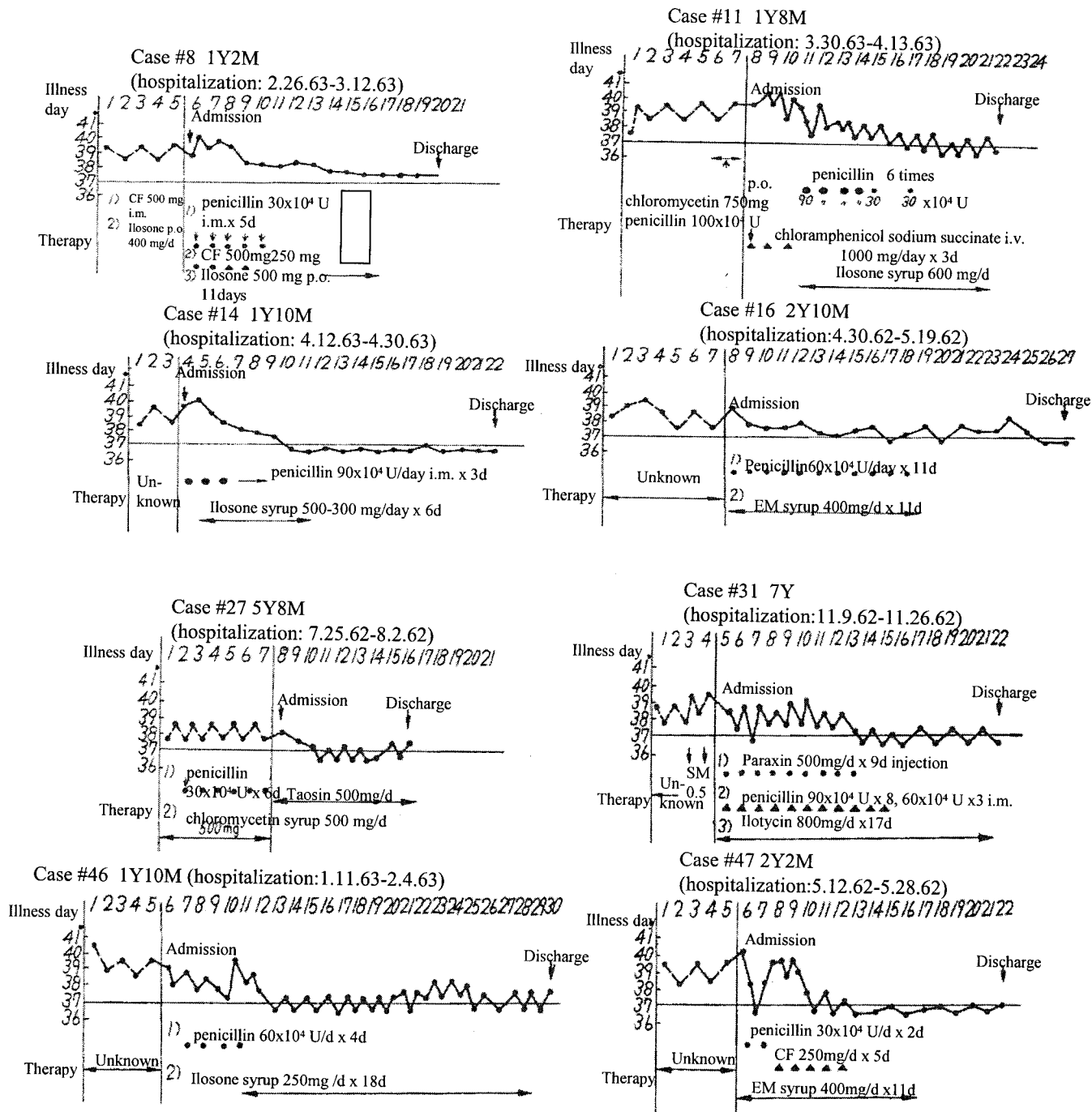


have never been treated with any antibiotic, except relatively mild cases or just by total accident. This question will be answered as more time passes by and accidents accumulate.

6. ETIOLOGY

This syndrome is a general, acute febrile disease. Its onset is acute, accompanied by cervical lymphadenopathy in most cases, and it does not recur. These features made me think of an infectious disease, so I tried to search for the cause by various means as I describe in this paper. However, it is difficult to decide whether this is caused by a specific bacterium or virus or is mediated by an allergic reaction to an infection or some autoimmune mechanism.

Table 55. Cases treated with penicillin (8 cases)

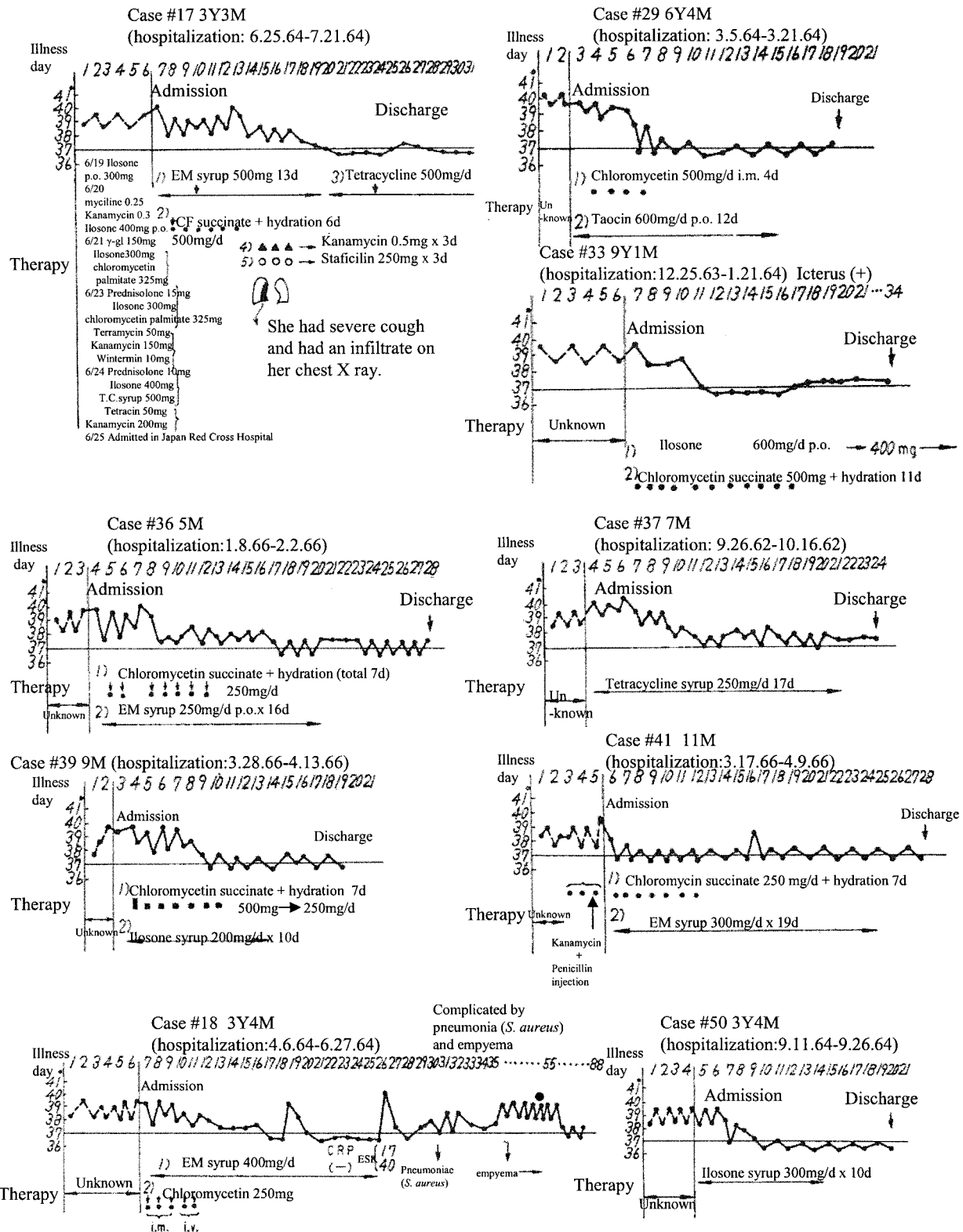


a. Hypothesis: specific viral infection. In our syndrome, the following characteristics are found: (1) no bacteria can be isolated from either blood cultures or from puncture of cervical lymph nodes; (2) this is an acute, general, nonsuppurative inflammation that can be accompanied by aseptic meningitis and hepatitis; (3) no recurrence was observed and patients recover within ~3 weeks; and (4) no known viruses have been

isolated. Thus I suspect this may be caused by a novel viral infection, and I am pursuing this direction in a collaboration with Dr. Ashiwara at the National Institute of Infectious Diseases.

b. Hypothesis: bacterial infection. In our syndrome, the following characteristics are found: (1) cervical lymphadenitis is acute, mostly unilateral, localized and not generalized, suggesting bacterial infection

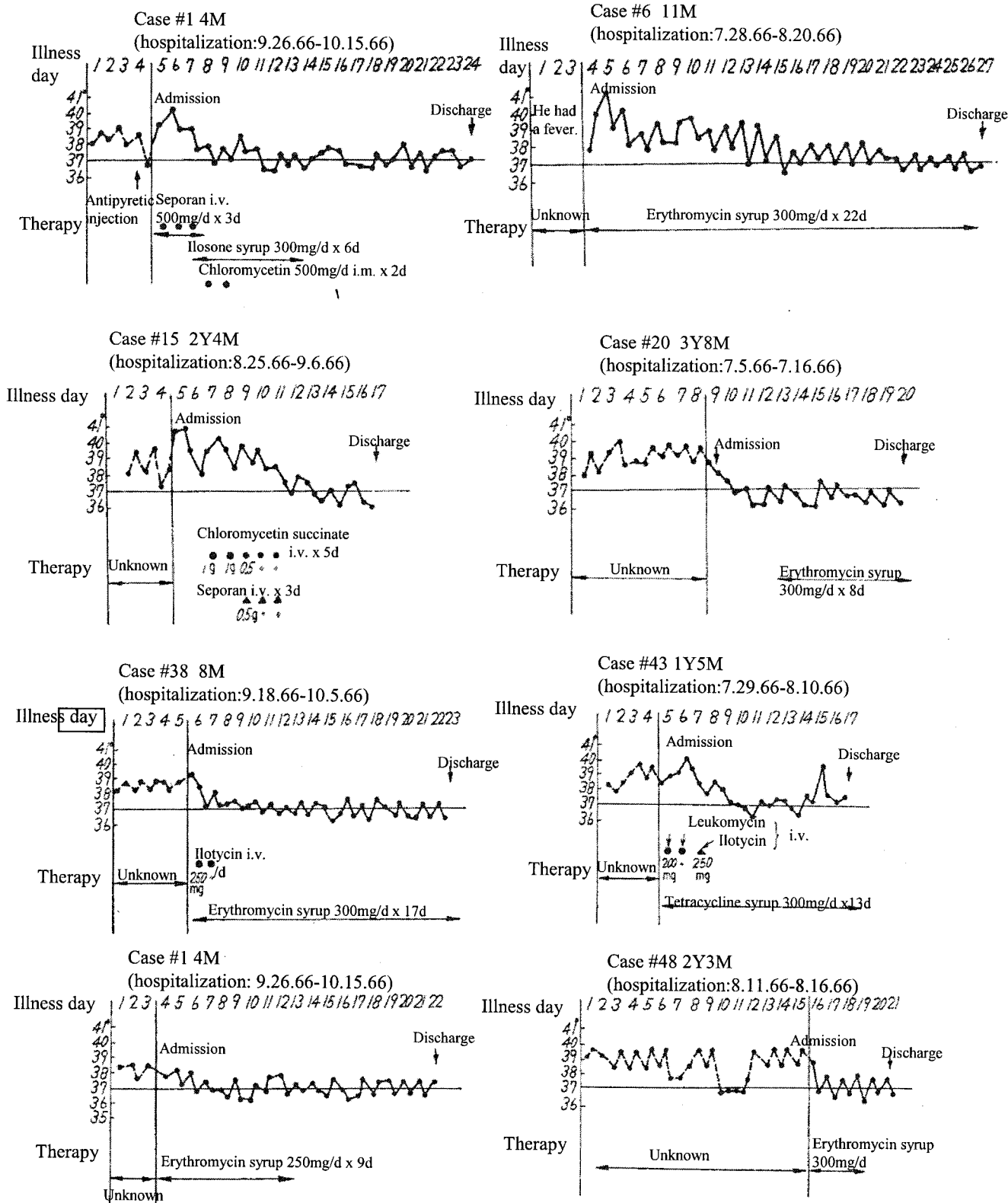
Table 56-1. Cases treated with antibiotics other than penicillin (17cases)



from the pharynx; (2) leukocytosis, left shift and accelerated ESR suggest bacterial infection rather than

viral infection; (3) generally most viral diseases with rash cause fever for only 1 week.

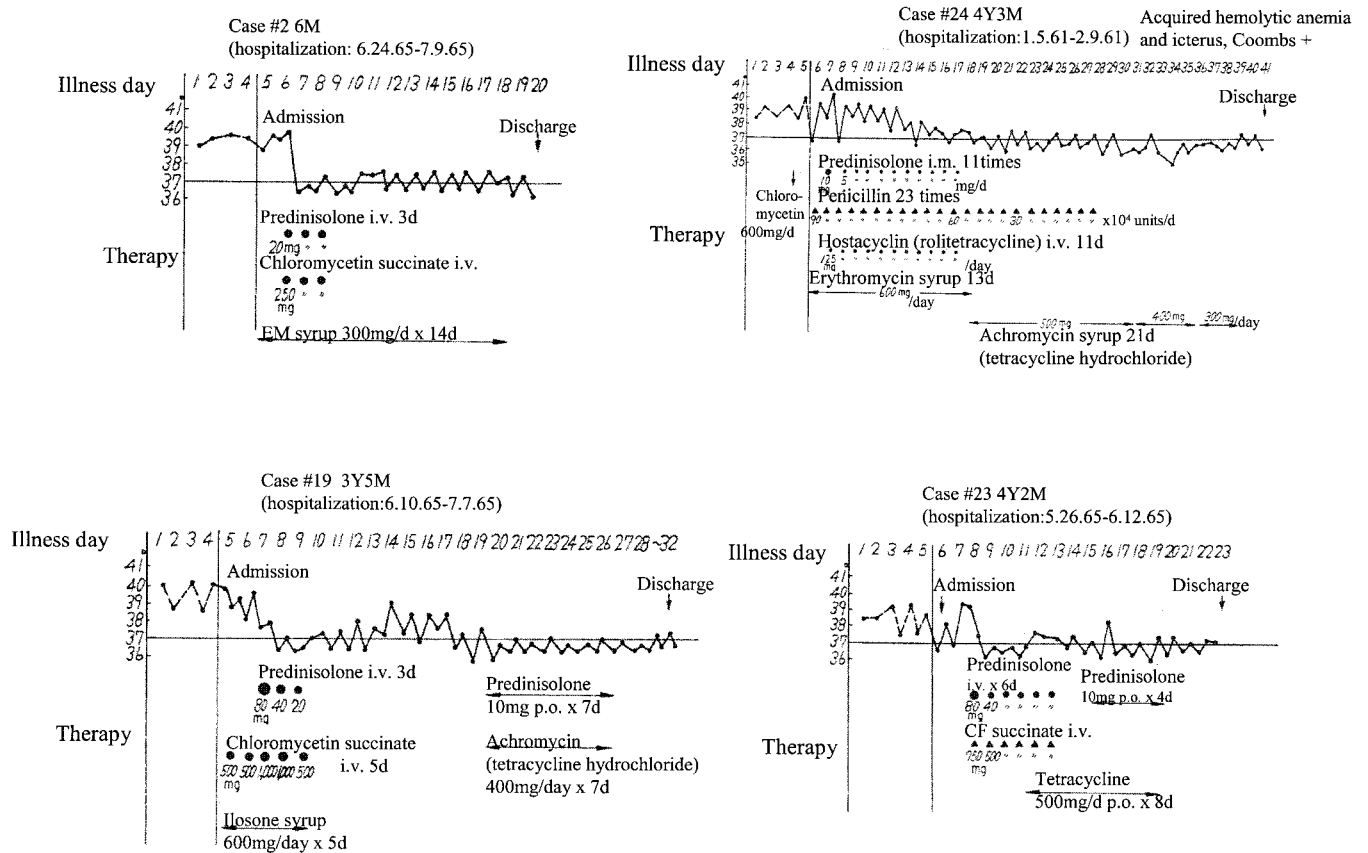
Table 56-2. Cases treated with antibiotics other than penicillin.



The bacterial infection theory is supported by the reasons above. However, there is no tendency toward

suppuration, no bacterial isolates have been recovered from cervical lymph nodes or blood and no focus

Table 57-1 Cases treated with steroids (i.v.: 8 cases, i.m.: 1 case)



of bacterial infection has been found. Thus it is difficult to be persuaded by this simple bacterial infection theory.

c. Hypothesis: an allergic reaction to an infection or autoimmune-mediated mechanism. The mechanisms of collagen vascular diseases such as rheumatic fever, [systemic] lupus erythematosus (SLE) or polyarteritis nodosa (PN) are not well understood. The possibility of an allergic reaction to a nonspecific bacterium or autoimmune disease has been pursued and discussed. In our syndrome no virus or bacterium has been isolated, so we need to consider the possibility of collagen vascular or related disease. In fact we recently experienced two cases of infantile PN and reported that the clinical features are extremely similar to the ones of this syndrome.⁵³ Generally in collagen diseases, the clinical course is chronic, there is a relatively poor prognosis and treatment with steroids is always necessary. Because of these features it seems as though our syndrome is very different. On the other hand there are some similarities, as has already been described. Moreover (1) the Coombs test can be positive, (2) the RA test can be positive and (3) there is an abnormal histology in the cervical lymph nodes with hyperplasia of endothelial cells in the postcapillary

venules and surrounding reticular cells. Studies along these lines remain as a future project.

7. DISCUSSION

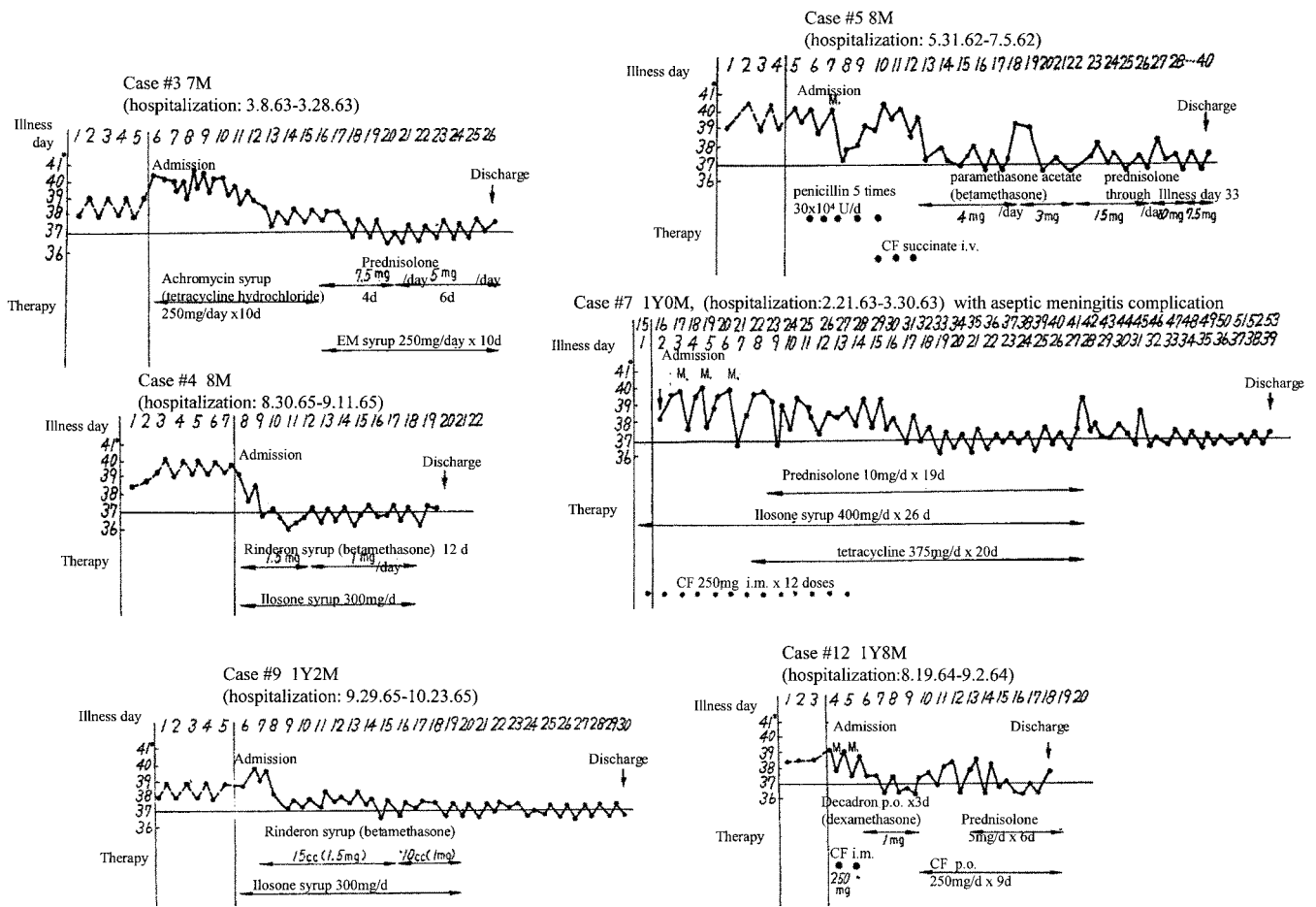
I have described the clinical features, laboratory data and treatment of the 50 cases I have experienced over the past 6 years. Now I need to compare our syndrome to similar diseases we already know.

1) Acute systemic febrile disease. *a. Sepsis.* In our syndrome (i) no bacteria have been found in the blood stream, (ii) no bacteria have been confirmed from cervical lymph nodes, which is considered to be a focus, and (iii) no metastatic infection can be found. Thus there are no data to suggest sepsis.

b. Rheumatic fever. In our syndrome (i) there is a weak relationship with streptococcal infection, (ii) no cases with a complication of carditis and none of the major Jones criteria are found, (iii) there are no recurrent cases and (iv) age distribution is different. For these reasons rheumatic fever can be eliminated as a possibility.

c. Rheumatoid arthritis (or Still's disease). In our syndrome there is (i) no chronic course, no recurrence, no persistent arthritis and (ii) no splenomegaly. For

Table 58-1 Cases treated with oral steroids (13 cases)



these reasons rheumatoid arthritis is different from our syndrome.

d. *Subsepsis allergica Wissler (SaW)*. In our syndrome (i) there is no intermittent fever over a month, (ii) there is no recurrent rash, (iii) peeling is special type from the tip of fingers and toes, (iv) there are no cases with cardiac disorder and (v) most cases with decreased eosinophil count in the blood stream. Thus our syndrome is different from SaW.¹²

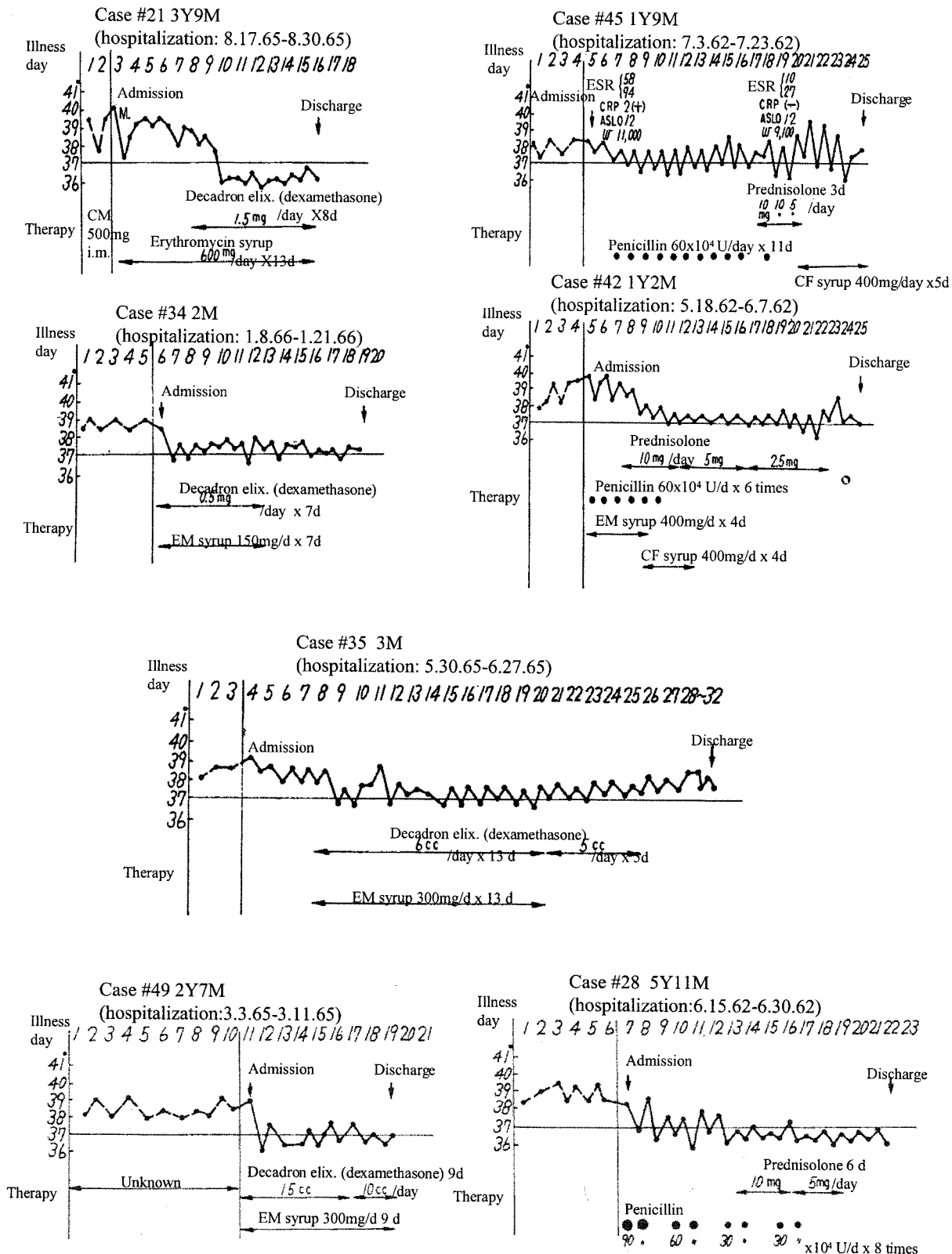
2) Viral infection with rash. It is clear that this is not a classical viral infection with rash, such as measles, rubella or chickenpox. In recent years many rash diseases caused by new viruses have been reported. As described by Nakao¹³ and Watanabe,¹⁴ the features of the disease caused by viral infection such as Coxsackievirus type A and B, echovirus, adenovirus or reovirus have (i) a relatively short duration of fever, (ii) a different pattern of rash and (iii) no peeling. Therefore these features do not fit with our syndrome. However, I need to mention about hand, foot and mouth disease,^{15, 16} which has similarity in the site of the rash. Hand, foot and mouth disease is a disease with a distinctive rash, as its name suggests, forming small vesicles on the hand, foot and oral mucosa and almost certainly caused by Coxsackievirus A16. In

our syndrome the rash never forms vesicles, clearly making it different from hand, foot and mouth disease. However, Gohd et al.¹⁷ reported a 16-month-old girl with Coxsackievirus A16 infection who presented with symptoms very similar to our syndrome. However, this is not the usual presentation of this type of viral infection, even though there may be some exceptional cases with echoviral or adenoviral infection like the case reported by Gohd. Considering these points, our syndrome is clearly different from any known viral infection with rash.

3) Pediatric disease with desquamation (most important). Skin desquamation in our syndrome is so distinctive that it serves as a key to diagnosis. Therefore we need to consider the other pediatric diseases with desquamation in our differential diagnosis.

a. *Scarlet fever.* The pattern of desquamation in our syndrome is very distinctive. It always starts from the junction of the skin, and the fingernail and the membranous desquamation is limited to both hands and feet, as previously described. Such a description can only be found in chapters on scarlet fever. In the scarlet fever chapter of the pediatric textbook by Brenne-mann,¹⁸ "Desquamation begins on the neck, chest, or upper back and not infrequently is first noted on

Table 58-2 Cases treated with oral steroids



fingers or toes at the junction of nail and skin under the nail." This description perfectly matches the desquamation pattern of our syndrome. Also in the chapter of

scarlet fever in both pediatric textbooks by Pfaundler and Schlossmann¹⁹ and Fanconi, it is written that "diagnostisch wichtig ist die Schuppung an den Finger

Table 59-1 Medications used in cases treated with steroids (22 cases)

Case	Prednisolone		dexamedhasone p.o.	betamethasone p.o.	paramethasone acetate p.o.	penicillin i.m.	penicillin p.o.	cefalotin p.o.	erythromycin sodium i.v.	erythromycin i.v.	erythromycin p.o.	chloramphenicol p.o.	kanamycin sulfate i.m.	Seporan I.V.	kitasamycin p.o.	total number					
	i.v.	p.o.																			
#2	•															2					
#3	•															2					
#4		•														1					
#5			•													4					
#7	•															3					
#9	•															1					
#12	•		•													4					
#19	•	•														4					
#21			•													1					
#23	•	•														4					
#24	•															4					
#25	•		•													5					
#26	•															4					
#28	•															4					
#32	•															2					
#34	•		•													5					
#35			•													1					
#40	•		•													1					
#42	•															2					
#45	•															3					
#49			•													3					
#30	•															1					
	8	10	1	7	1	1	6	2	1	1	6	7	3	4	1	1	1	1	1	1	5

Table 59-2 Medications used in cases treated without steroids (28 cases)

Case	Penicillin i.m.		erythromycin i.v.	teracycline p.o.	chloramphenicol i.m.	kanamycin sulfate i.m.	Staficillin i.m.	Taoicin p.o.	Seporan I.V.	kitasamycin i.v....	total numbers										
	p.o.	i.v.																			
#8	•										2										
#10	•										2										
#11	•										2										
#13	•										2										
#14	•										2										
#16	•										2										
#17	•										2										
#18	•										2										
#27	•										2										
#29	•										2										
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#33	•										2										
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#37	•										2										
#39	•										2										
#41	•										2										
#46	•										2										
#47	•										2										
#50	•										2										
#15											1										
#43											1										
#44											1										
#22											1										
#20											1										
#48											1										
#6											1										
#1											1										
#38											1										
	7	20	2	3	1	1	1	2	2	1	1	1	1	1	1	1	1	1	1	1	1

und Zehenspitzen, die auch bei geringer Abschuppung nicht fehlt." Therefore if we just focus on the pattern of desquamation, our syndrome corresponds very well with scarlet fever. However, in our syndrome there is (i) very little relationship with *Streptococcus*, (ii) different types of rash, (iii) rarely recognized pharyngitis (at the time of hospitalization) and no complication of nephritis, (iv) no effectiveness of penicillin and (v) a younger age group. Thus scarlet fever is eliminated.

Table 60. Drug allergy testing (4 cases)

Case #	Illness day of test	Duration of test (days)	Clinical reaction
39	14-19	6	none
36	88-93	6	none
9	20-24	5	none
26	12-20	9	none

b. *Izumi fever*. In our syndrome (i) there are no apparent epidemics, (ii) there are different types of rash [with no secondary rash and (iii) the age group is different.

c. *Erythema scarlatiniforme desquamativum recidivans or erythema scarlatiniforme*.²⁰ In our syndrome (i) there are no recurrent cases, (ii) desquamation starts mainly in the second disease week and (iii) there are leukocytosis and strawberry tongue. Therefore it is different from erythema scarlatiniforme desquamativum recidivans or erythema scarlatiniforme.

d. *Drug rash*. It is not clear about the relationship between this syndrome and drugs, because in many cases we did not have very precise information about the drugs used before hospitalization. Therefore in four cases we performed allergic drug testing with penicillin G (200 000 to 400 000 U/day), probenecid, sulfamethoxazole, chloramphenicol and a mixture of sulpyrine and sulfisomidine, but all challenges were clinically negative (Table 60). Also the fact that no recurrent cases were recognized among the 50 cases suggests that the possibility of drug rash is very small.

e. *Toxic rash*. For drug rash or toxic rash, if the cause is not clear, these classifications are more or less imaginary or hypothetical and are not certain. In any case, when a dermatologist looked at our cases, he said, "We would diagnose this as a toxic rash, if we looked at only one case and mentioned only about the rash. But if we consider the other important symptoms as well, this is not a simple toxic rash, but a syndrome with certain clinical features." (Dr. Kakiuchi, the chief dermatologist at our hospital and Dr. Morio Nishiyama, dermatologist at Kanto Teshin Hospital).

f. *Gianotti-Crosti syndrome*.^{21, 22} This syndrome is also called acrodermatitis papulosa infantum or histologically reactive subacute reticuloendotheliitis, which is a disease of infants with rash and desquamation. However, our syndrome is different in the following ways: (i) the pattern of rash and (ii) no specific cutaneous histologic finding as in Gianotti-Crosti syndrome.

4) **Mucocutaneous-ocular syndrome (MCOS)**. Proppe combined "dermatostomatitis (Baader). ectodermosis erosiva pluriorificialis (Fiessinger und Rendu)," "Stevens-Johnson syndrome" and "conjunctivitis et stomatitis pseudomembranacea" into one category called "Syndroma muco-cutaneo-oculare acutum Fuchs" discriminating so-called erythema erosiva multiforme (Eem) without mucosal disorder by Hebra.²³ At the same time in the same paper, he is also discriminated "ophthalmia lente" (Gilbert, 1920²⁴) and *Tri-symptomenkomplex* (Behçet, 1937²⁵) from "periodisch

rezidivierendes muco-cutaneo-oculares Syndrom” in this report. But according to Proppe this naming is already done by Franceschetti and Valerio (1939–1940) as *Gilvert'sches muco-cutaneo-oculares Syndrom* or *Fuchs'sches syndrome*.

Probably the naming of “mucocutaneous-ocular syndrome” was first made by Franceschetti and Valerio between 1939 and 1940. Historically those syndromes were divided into two groups: one was a subtype of so-called erythema erosiva multiforme reported by Hebra²³ (1866), Fuchs (1876), Duhring²⁶ (1896), Rendu²⁷ and Fiessinger et al.²⁸ (1916, 1923), Stevens and Johnson²⁹ (1922), Baader³⁰ (1925) and Proppe³ (1948), and the other was the so-called Behçet syndrome and its related diseases reported by Bietisch^{31, 39} (1879), Neumann (1894), Gilbert²⁴ (1920), Behçet (1937) and Franceschetti and Valerio (1939–1940). In 1954 Schreck³² analyzed both groups from the standpoint of an ophthalmologist. He called the first group of diseases cutaneo-muco-oculoepitheliale syndrome, because of its primary involvement of the ectodermal system such as conjunctivae and cornea, and the second group of disease as cutaneo-muco-uveale syndrome, because of its primarily involvement of the mesodermal system such as Mesodermale Tunica vasculosa des Auges (Uvea). The classification of Schreck gave an embryologic reason and made the difference more distinctive for each group of diseases, even though it focused on only one aspect of the pathology.

In 1950 Robinson³³ reported his own 11 cases with a literature review; analyzed 4 cases of Behçet's disease, Stevens-Johnson disease, Reiter's disease³⁴ and ectodermosis erosiva pluriorificialis (Eop) as mucocutaneous ocular syndrome; and considered them as variants of Eem, except Reiter's disease. However, this understanding is not very accurate, notwithstanding the paper by Schreck.

As shown above the name MCOS was quite convenient but had the problem of lumping together so many clearly clinically different diseases under the same name. Also in the reports in Japanese, Kobayashi,³⁵ Nishihara³⁶ and Sakata³⁷ reported cases of EemS [erythema erosiva multiforme syndrome] as MCOS, whereas Hurusawa et al.³⁸ reported true cases of Behçet's disease under the same name of MCOS. This is a problem.

Therefore when the general study group of the Ministry of Education started a “study of mucocutaneous-ocular syndrome” in 1958, their first goal was the organization of this syndrome, which seemed very appropriate. As a result MCOS was divided into three groups: (1) erythema erosiva multiforme syndrome; (2) Behçet's disease; and (3) Reiter's disease. From this study Dr. Nishiyama emphasized that Behçet's disease should be treated as a disease independent from EemS.

If we use this classification our syndrome is most similar to EemS.

Now let us look at textbooks to learn how they describe EemS. In the textbook by Fanconi,⁴⁰ it is divided into two groups: (1) ectodermosis pluriorificialis; and (2) erythema exudativum multiforme [Eem]. The former group is again divided into three groups: *Eem mit Shleimhautbeteiligung*; *Übergangsform*; and *Pluriorificielle Ektodermose*. In the textbook by Nelson⁴¹ EemS is treated as one entity, erythema multiforme exudativum (Stevens-Johnson syndrome), and especially the severe type with involvement of the mouth and anus was called Eem pluriorificialis. In the textbook by Ormsby⁴² it is divided into erythema multiforme and ectodermosis erosiva pluriorificialis. In the textbook of Sutton⁴³ it is divided into erythema multiforme and bullous malignant erythema multiforme. In *Handbuch der Haut und Geschlechtskrankheiten*,⁴⁴ it is divided into two main groups: (1) idiopathic Eem; and (2) mucocutaneous ocular syndrome. As shown above each author has a different classification scheme. We can see how variable the understanding of EemS can be. Maybe this is the result of each case being reported by different authors such that the reports are similar in some aspects but different in others when compared with the representative reports starting with Hebra, Fuchs, Duhring, Rendu, Fiessinger, Stevens-Johnson and Baader. All of this confusion originates from the unknown etiology of these conditions. In comparing our cases with all these descriptions in previous reports and in the textbooks, none was identical. Especially different was the age distribution; 21 cases in the literature analyzed by Soll⁴⁵ in 1947 contained 11 cases between the age of 2 and 9 [years], but no infantile cases. Eighty-one cases reviewed by Ashby⁴⁶ in 1951 included only 2 cases under the age of 3 years, but no infantile cases. Katsura⁴⁷ reported 54 cases of EemS in a series of 119 cases of MCOS in 1957, but only 2 cases were under 1 year old, 9 cases were between 1 and 5 years old, and 4 cases were between 6 and 11 years old, again demonstrating the low frequency in infants. The report by Ide et al.⁴⁸ in 1959 had 4 cases under the age of 2 years of >200 cases. The report by Takahashi and Nakano⁴⁹ in 1961 had 100 cases of EemS of 200 cases of MCOS and only 3 cases under 2 years of 20 cases under 10 years. In the report of Clexton⁵⁰ in 1963, which described 31 cases between 2 and 72 years of age, there was no description of infantile cases, whereas 11 of 31 cases were under the age of 9 [years]. According to the textbook of Fanconi cited previously, ectodermosis pluriorificialis is more frequent among *spätere Kleinkindesalter*. All those showed that conventional MCOS or EemS is very rare among young infants and children under 2 years. Itoga and Yamagishi⁵¹ in 1960 in a paper entitled, “Experience of treatment for pediatric mucocutaneous-ocular syndrome with pituitary adre-

nal gland hormone" described 14 of 20 cases (70%) under the age of 2 [years], and this is very distinct compared with the other reports, pointing out the characteristics of age distribution of this syndrome. Their report was the only one that focuses on MCOS under 2 years, as far as I could find. The cases reported by them are very similar to our cases in many features. However, there are several important clinical differences, which are described:

1. *Cutaneous symptoms.* The authors wrote, "Erythema, papules, vesicles, and desquamation were recognized all over the body during whole course in all the cases, sometimes new and old lesions were seen simultaneously." In our syndrome desquamation sometimes started in the presence of erythema but never formed vesicles. This is an extremely important difference in the cutaneous findings. Regarding desquamation, they wrote, "Various levels of desquamation started at the same time when new rash stopped appearing any more, and the desquamation lasted over a few days to more than 20 days." In our syndrome desquamation is very specific, starts from the junction of nail and skin and never occurs other than on the hands or feet.

2. *Ocular symptoms.* They wrote, "We recognized conjunctivitis or conjunctivitis-like findings in all the cases." But in our cases it was not a simple conjunctivitis, but rather a part of a general reaction of vasoconnective tissue. Characteristic findings were bilateral injection of the bulbar conjunctivae (or actually dilatation of capillary vessels).

3. *Mucosal symptoms.* They wrote, "Findings of mucus membranes are pseudomembrane in 1 case and aphthae, bleeding, ulcer, and candidiasis in 10 cases." In our cases we noted only dryness, redness, erosion and cracking of lips and diffuse injection of whole oral mucosal membrane, which never formed aphthae, ulcers or pseudomembrane.

4. *Cervical lymphadenopathy.* In their cases lymphadenopathy was recognized in 7 cases (35%). In our cases it was seen twice as frequently (33 cases, 66%).

Those are the differences when our cases were compared with the cases reported by Itoga and Yamagishi. Until now I have discussed the relationship of our syndrome to MCOS or EemS, but now it is necessary to look at the table of *Polymorphe Ectodermose* made by Wechselberg⁵² in 1954 based on the classification of Glanzmann and Fanconi. The notion of *Ectodermose erosive pluriorificielle typus 1* by Glanzmann, *Übergangsform* by Fanconi and *Leichte-mittelschwere Übergangsform* in this table may have important meaning for the future classification of our syndrome. However, at this time I have reported the clinical findings as they are of a syndrome that is seen only in a certain age group and presents with certain specific clinical findings, without trying to decide its affiliation with any of the already known diseases or syndromes. As to the

cause of this syndrome, it is now under investigation so the plan is to report the cause as a second report in the future.

CONCLUSION

I report here the clinical characteristics, laboratory data and effectiveness of treatment in 50 cases with an acute febrile erythematous syndrome. The characteristics of this syndrome, which occurs mainly in infants, are cervical lymphadenopathy, bilateral injection of the bulbar conjunctivae, dry red lips with erosion or cracking, diffuse injection of the oral mucosa and desquamation of the fingers and toes. As a result of a literature review, I have also discussed the possibility that this syndrome does not belong to the any disease ever reported.

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