Systemic Capillary Leak Syndrome

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Abstract

A 40-year-old woman was referred to our hospital with severe hypovolemic shock and anasarca. The laboratory findings showed marked hemoconcentration and a decrease in total serum protein with the presence of monoclonal IgG- λ . She had had a similar episode of generalized edema 2 years previously. We diagnosed the patient as having typical systemic capillary leak syndrome (SCLS) and she improved gradually after infusion of albumin-containing fluid. SCLS is a very rare condition caused by unexplained episodic capillary hyperpermeability. Its treatment has remained largely supportive and the prognosis is generally poor. Awareness of SCLS is necessary for improvement of the outcome.

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Key words: capillary hyperpermeability, hypovolemic shock, prognosis

Introduction

Systemic capillary leak syndrome (SCLS) is a rare condition characterized by unexplained episodic capillary hyperpermeability. This phenomenon produces a shift of fluid and protein from the intravascular to the interstitial space, with subsequent hypovolemia, hemoconcentration and hypoproteinaemia. The pathogenesis of this disorder has not been elucidated and its clinical outcome is generally poor. We describe here a typical case of SCLS that was manageable by prompt treatment, and review the literature.

Case Report

In February 1998, a 38-year-old Japanese woman was admitted to Ojiya Hospital with generalized edema and oliguria after a flu-like illness. Laboratory data showed a marked increase in hematocrit (55.2%), and a decrease in total serum protein (4.9 g/dl) without proteinuria. She was treated with in-

travenous infusion of fluids, including albumin and a diuretic drug, and the edema and laboratory abnormalities improved in a few days. Thereafter, however, she developed mild bilateral leg edema recurrently in the premenstrual period or during the menstruation. She had a history of iron deficiency anemia since the age of 24 years, but the condition had not been treated. In 1991 she was diagnosed as having bilateral thyroid tumors. She received vaccine therapy over several months, but the details of the treatment were not available.

On February 24, 2000, she was admitted to Ojiya General Hospital again because of shock and anasarca after a flu-like illness of 3 days' duration. The laboratory findings also showed marked hemoconcentration and a decrease in total protein. She was treated with intravenous fluids, albumin and dopamine immediately, but hypotension and oliguria persisted and she was transferred to our hospital on February 25. On arrival, she was fully conscious. Her body weight was 60 kg, 2 kg more than usual. The systolic blood pressure was 80 mmHg, and the body temperature was 36.8°C. Lymphadenopathy was not evident. A large goiter was recognized in the thyroid gland. A chest and abdominal examination showed no abnormal findings. Her extremities were cold, pale and markedly edematous.

The results of laboratory tests on admission are summarized in Table 1. Blood cell counts revealed an increase in both hematocrit (49.9%) and hemoglobin (16.8 g/dl). White blood cell count had increased to 21,800/ μ l, with a normal fraction. Although a marked decrease in total serum protein was observed (4.4 g/dl), urinalysis showed no proteinuria. Blood urea nitrogen and creatinine had increased to 50.7 mg/dl and 1.25 mg/dl, respectively. Serum levels of IgG, C3 and C4 had decreased. IgA and IgM levels were normal. Thyroid function test was normal. Monoclonal immunoglobulin G- λ was detected in the patient's serum by immunoelectrophoresis, but Bence Jones protein was negative. Bone marrow aspiration was not conducted, at the patient's request. A chest X-ray film revealed no pleural effusion, pulmonary congestion or cardiomegaly. Ultrasonographic examination of the abdomen revealed no ascites.

On the day of admission, intravenous administration of over 4.5 liters of fluid with 5% albumin was started immediately, together with dopamine (8 μ g/kg/min) and dobutamine (5 μ g/

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Table 1. Laboratory Data on Admission to Our Hospital

<i>Peripheral blood</i>					
White blood cell count	21,800/ μ l	Ca	9.1 mg/dl	CH ₅₀	37.7 U/ml
(Neutrophil)	71.8%	P	5.8 mg/dl	Complement C3	43 mg/dl
(Eosinophil)	0.8%	Aspartate aminotransferase	12 IU/l	Complement C4	11 mg/dl
Red blood cell count	674 $\times 10^4$ / μ l	Alanine aminotransferase	10 IU/l	<i>Endocrinology</i>	
Hemoglobin	16.8 g/dl	Lactate dehydrogenase	98 IU/l	Serum Free T3	1.78 pg/ml
Hematocrit	49.9%	Alkaline phosphatase	90 IU/l	Serum Free T4	1.13 ng/ml
MCV	74.0 fl	Creatine phosphokinase	96 IU/l	Serum TSH	0.91 μ U/ml
Platelet	33.5 $\times 10^4$ / μ l	Glucose	201 mg/dl	<i>Urinalysis</i>	
ESR	18 mm/h	<i>Serology</i>		Sugar	(-)
<i>Biochemistry</i>		C-reactive protein	0.6 mg/dl	Protein	(-)
Total protein	4.4 g/dl	Immunoglobulin G	497 mg/dl	Occult blood	(-)
Albumin	3.0 g/dl	Immunoglobulin A	115 mg/dl		
Blood urea nitrogen	50.7 mg/dl	Immunoglobulin M	72 mg/dl		
Creatinine	1.25 mg/dl	Immunoglobulin E	30.3 U/ml		
Na	126 mEq/l	Antinuclear antibody	negative		
K	4.1 mEq/l	Immuno-electrophoresis	IgG- λ		
Cl	97 mEq/l				

MCV: mean corpuscular volume, ESR: erythrocyte sedimentation rate, CH₅₀: complement hemolysis 50, T3: triiodothyronine, T4: thyroxine, TSH: thyroid stimulating hormone.

kg/min). The patient's systolic blood pressure returned to normal within 12 hours. Urine volume increased and the anasarca improved gradually without diuretics. The dosages of intravenous fluids and cardioactive agents were tapered and the infusion was stopped on March 1. Ten days later, her weight had decreased to 54.7 kg and no edema was present. The hemoglobin level was 9.0 g/dl and total serum protein had increased to 6.9 g/dl (albumin 4.6 g/dl). The serum levels of immunoglobulin and components of complement returned to normal.

We diagnosed the patient as having SCLS because of the decrease in serum protein and the increase in the hematocrit during the acute episodes of anasarca and hypotension and monoclonal gammopathy. To prevent the disease flaring, we began administration of theophylline (400 mg twice daily) in March 2000. She has continued this medication without any episode of anasarca or hypotension up to February 2001, although mild edema has developed occasionally. The patient's anemia improved with iron replacement therapy. Cervical CT scan and aspiration biopsy of the bilateral thyroid tumors (left, 5 cm diameter, and right, 2 cm diameter) revealed adenomas, which were followed up carefully.

Discussion

Idiopathic SCLS was first described by Clarkson et al (1) in 1960. Since then, 57 cases have been described in the literature, with only three cases in Japan (including the present case) to our knowledge. It is a rare condition characterized by unexplained episodic capillary permeability due to a shift of fluid and protein from the intravascular to the interstitial space. This results in recurrent episodes of generalized edema and hypovolemic shock, with hemoconcentration and hypoproteinemia.

It is well documented that most of the reported cases have been associated with monoclonal gammopathy. No patients exhibited any evidence of amyloidosis or endocrine disease during their remissions. The present patient had suffered recurrent attacks of edema and presented suddenly with shock and anasarca associated with marked elevation of hematocrit, hypoproteinemia and monoclonal gammopathy. These are typical features of SCLS.

The reported cases of SCLS in the literature (from 1960 to 2000) are summarized in Table 2. The condition primarily affects healthy young and middle-aged adults (age range: 9 to 67, mean age $\pm$ SD: 46.1 $\pm$ 13.3) with equal distribution between the sexes (male: 28, female: 27, unknown: 1). Forty-seven patients (82%) had a monoclonal immunoglobulin, predominantly IgG κ , in their serum. No case had a relevant familial history. Although the precise mechanism of SCLS has not been elucidated, Amoura et al (2) suggested that viral infection might trigger the attacks because many of the patients had experienced preceding episodes of flu-like illness. The present case supports this; our patient had attacks after a flu-like illness. Menstruation has been incriminated as a trigger of acute episodes (1), again as seen in our patient. As described above, most patients with SCLS have a monoclonal immunoglobulin in their serum. These findings suggest that paraproteins might have a role in inducing capillary hyperpermeability, but this has not been demonstrated. On the other hand, conditions closely resembling SCLS have been observed in patients receiving recombinant interleukin 2 (IL-2) therapy (3, 4). This observation has provided a clue to the mechanism of SCLS and it has been hypothesized that cytokines, most notably IL-2, cause endothelial damage and capillary hyperpermeability (5, 6). The presence of IL-2-receptor positive cells and perivas-

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Table 2. Reported Cases of SCLS

Case	Year (Reference)	Age	Sex	Monoclonal component	Therapy	Out come
1	1960 (1)	32	F	IgG	steroid	died after 3 years
2	1963 (14)	45	M	IgG	?	?
3	1967 (15)	52	M	normal	fluid therapy	died after 4 years
4	1969 (16)	45	F	IgGκ	?	died after 3 years
5	1973 (17)	47	M	+	?	died after 8 years
6	1975 (18)	40	M	IgGκ	?	alive for 6 years
7	1977 (19)	40	M	IgGλ	fluid therapy	died after 3 years
8	1978 (20)	37	F	IgGκ	fluid therapy	?
9	1979 (21)	43	M	IgGλ	terbutaline	alive for 4 years
10	1981 (22)	69	M	IgGκ	steroid	alive for 0.5 years
11	1981 (23)	?	?	IgGκ	?	?
12	1982 (24)	22	F	?	?	?
13	1983 (25)	21	F	?	fluid therapy	died after 1 year
14	1985 (26)	63	F	IgG	fluid therapy	?
15	1986 (27)	45	M	IgG	fluid therapy	?
16	1986 (28)	37	F	IgGκ	fluid therapy	alive for 10 years
17	1987 (29)	37	M	IgGκ	fluid therapy	alive for 6 years
18	1987 (29)	44	F	IgGκ	fluid therapy	alive for 5 years
19	1987 (30)	33	M	IgGκ	T+A, IVIg	alive for 6 years
20	1988 (31)	49	M	IgGκ	?	alive for 5 years
21	1988 (32)	39	F	IgGκ	PEX, MP	alive for 4 years
22	1988 (33)	39	M	IgGκ, λ	terbutaline	died after 5 years
23	1988 (34)	55	F	?	fluid therapy	?
24	1989 (35)	46	M	IgGκ	fluid therapy	died after 1.5 years
25	1990 (7)	52	F	IgGκ	fluid therapy	alive for 3 years
26	1990 (36)	37	M	normal	fluid therapy	?
27	1990 (36)	44	F	IgGλ	fluid therapy	?
28	1992 (37)	65	M	IgAλ	T+A	alive for 10 years
29	1992 (37)	56	M	IgGκ	T+A	alive for 5 years
30	1992 (37)	58	F	IgGκ	T+A	alive for 3 years
31	1993 (38)	36	M	IgGκ	steroid	alive for 6 years
32	1994 (4)	19	M	normal	antibiotics	?
33	1995 (39)	46	M	hypoglobulin	Ca antagonist	?
34	1995 (9)	34	F	IgGκ	steroid	died after 3 years
35	1995 (40)	9	F	normal	fluid therapy	?
36	1995 (41)	56	F	IgGκ	T+A, IVIg, steroid	alive for 3 years
37	1995 (13)	67	F	IgGκ	T+A	alive for 1 years
38	1997 (2)	49	F	IgGκ	T+A	alive for 6 years
39	1997 (2)	53	M	IgGκ	T+A	alive for 2 years
40	1997 (2)	35	M	IgGκ	T+A, steroid, cyclosporine indomethacin, diuretics	alive for 7 years
41	1997 (2)	61	M	IgGκ	T+A	alive for 4 years
42	1997 (2)	53	M	IgGκ	steroid	?
43	1997 (2)	44	M	IgGκ	T+A, cyclosporine	alive for 6 years
44	1997 (2)	63	F	IgGκ	T+A	alive for 4 years
45	1997 (2)	64	M	IgGκ	T+A, PEX, MP	died after 4 years
46	1997 (2)	53	F	IgGκ	Gingo biloba	died after 10 years
47	1997 (2)	49	F	IgGλ	MP	alive for 6 years
48	1998 (42)	34	M	IgGκ	?	?
49	1998 (43)	30	F	IgGκ, λ	steroid	alive for 2 years
50	1999 (12)	28	M	IgGκ	T+A	died after 2 years
51	1999 (12)	51	F	IgGκ	T+A	alive for 11 years
52	1999 (12)	39	F	IgGλ	T+A	alive for 10 years
53	1999 (12)	47	M	normal	T+A	alive for 6 years
54	1999 (12)	66	F	normal	T+A	alive for 4 years
55	2000 (44)	64	F	IgGκ	theophylline, steroid diuretics	alive for 7 years
56	present case	39	F	IgGλ	theophylline	alive for 3 years

T+A: terbutaline+aminophylline or theophylline, IVIg: intravenous immunoglobulin, PEX: plasma exchange, MP: melphalan+prednisone.

cular infiltrates of CD8-positive lymphocytes surrounding damaged endothelial cells during attacks in one patient have also been reported (7). Our patient had received vaccine therapy for the thyroid tumors 7 years before the attacks. It is possible that such therapy might be associated with the development of SCLS. In most cases of IL-2-induced capillary leak syndrome, however, attacks developed during the IL-2 therapy (8), and therefore the etiology in our case remains unknown.

Most cases of SCLS have a history of shock state during the acute phase due to an increase in capillary permeability, and hypovolemic shock was quite severe in our patient. When the condition has been identified, immediate and adequate replacement therapy is necessary. Intravenous fluid therapy, including albumin, should be started for the hypovolemic shock. This is essential to maintain tissue perfusion and to protect organs from the effect of the shock. In the recovery phase, however, the fluids return to the intravascular space and there is a risk of pulmonary congestion (9). Various agents have been tried for treating this problem, but their efficacy remains controversial. Steroids and diuretics have given variable results. Loop diuretics might be useful for the normalization of intravascular fluid overload.

In addition to the treatment for the acute phase, several prophylactic therapies have been tried. Recurrence is a notable feature of SCLS, so prevention of this is important. Terbutaline and theophylline therapy have been reported to be apparently effective against of SCLS recurrence. Beta-2 stimulators (terbutaline or salbutamol) can inhibit macromolecular leakage during the normalization response (10). Theophylline has immunomodulatory and anti-inflammatory activities that are useful in antagonizing cytokine-mediated endothelial damage and capillary hyperpermeability (11). Tahirkheli and Greipp (12) followed eight patients with SCLS on a regimen of terbutaline and theophylline for a median period of 9 years and demonstrated prophylactic efficacy. But some reports have denied a prophylactic effect, and the efficacy of the regimen remains unclear. Our patient has continued theophylline therapy for one year without any further episode of anasarca and hypotension, but mild edema has developed occasionally. Because SCLS is a rare disease, it is very difficult to judge the efficacy of such a regimen. Other prophylactic treatments (prednisone, Ginkgo biloba, plasmapheresis, intravenous immunoglobulins, cyclosporine, etc.) have been tried, but their efficacy is also unclear.

Despite aggressive resuscitation and prophylactic treatments, this syndrome is often fatal. At least 12/56 patients (21.4%) died of the disease during follow-up. The causes of death were mainly shock and pulmonary congestion (8). In three patients, SCLS evolved into multiple myeloma, of which two of three patients died (2, 13).

In conclusion, awareness of SCLS is most important for improving the outcome because early diagnosis and immediate fluid replacement therapy are essential. Educating patients to visit the hospital as soon as generalized edema develops, especially following any flu-like illness, is also important.

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