

The Importance of Bacterial Superantigens Produced by *Staphylococcus aureus* in the Treatment of Atopic Dermatitis Using Povidone-Iodine

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Key Words

Povidone-iodine · Atopic dermatitis · Bacterial superantigen · Antitoxin IgE antibody · Disinfection therapy

Abstract

Atopic dermatitis (AD) is frequently associated with intestinal and cervical lesions. *Staphylococcus aureus* produces many kinds of toxins, the bacterial superantigens. The detection rate of toxins was 80.1% from 196 *S. aureus* strains. Neurological examinations revealed abnormalities in 59 out of 81 AD patients. Cervical magnetic resonance imaging (MRI) was performed in 46 patients randomly and showed abnormal findings in 38 of these patients. In 23 patients who underwent MRI and duodenal biopsy, 3 were found to be normal neurologically and 2 patients showed normal duodenal tissue. However, 18 patients had abnormal findings both on neurological examination and in duodenal tissue. Serial duodenal biopsy tests were performed in 10 AD patients. In 5 patients, the findings of chronic duodenitis disappeared after the therapy with povidone-iodine. These data indicate that the therapy was effective not only for the skin

lesions, but improved gastrointestinal tract lesions and cervical myelopathy, by eradicating bacterial superantigens.

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Objective

The efficacy of a combination of the conventional therapy for atopic dermatitis (AD) and the disinfection therapy against *Staphylococcus aureus* was evaluated. Moreover, effects of this therapy on lesions of the duodenum and spinal cord as well as on total IgE levels and antitoxin IgE antibodies were also assessed.

Method

We recommended that the AD patients apply 10% povidone-iodine solution on the skin rashes for 3 min and then wash it away with a warm shower. This treatment was to be repeated at least twice a day, and at least 4 times a day for the whole body, if possible, except for the face. Since the facial skin is very sensitive to stimuli, we recommended that the face should be disinfected twice a day using 1:6 diluted disinfection solution. After 2 min application, the disinfectant applied should be washed away. In addition,

Table 1. Results of skin culture from AD patients in 1995 and 2003

	MSSA	MRSA	CNS	MSSA + CNS	No growth	Total
1995						
Number	334	10	106	106	51	607
Percent	55.0	1.6	17.5	17.5	8.4	100
2003						
Number	60	5	34	12	8	119
Percent	50.4	4.2	28.6	10.1	6.7	100

MRSA = Methicillin-resistant *S. aureus*.

patients were recommended to wash the face using soap 4 times a day. Steroid ointment was applied once daily to the affected areas, and moisturizing ointment was applied continuously to maintain the affected areas moist and to protect the skin barrier from destruction [1].

Results

Results of Skin Culture

From the skin lesions of the 607 AD patients, *S. aureus* was isolated at a high incidence in 1995. Methicillin-sensitive *S. aureus* (MSSA) was isolated in 55% of the AD patients, coagulase-negative staphylococcus (CNS) in 17.5%, both MSSA and CNS in 17.5% and methicillin-resistant *S. aureus* in 1.6%. No growth was found in only 8.4%. MSSA, methicillin-resistant *S. aureus*, CNS and MSSA + CNS were isolated in 50.4, 4.2, 28.6 and 10.1% of the AD patients, respectively, in 2003. No bacterial growth was noted only in 6.7% (table 1).

Toxins Detected by PCR from *S. aureus*

S. aureus produces many kinds of toxins. Some strains produce several toxins, such as staphylococcal enterotoxin A (B, C, E), toxic shock syndrome toxin 1 and exfoliative toxin A (B). The detection rates of staphylococcal enterotoxins A, B, C and E were 9.7, 55.6, 7.7 and 30.6%, respectively. The detection rate of toxic shock syndrome toxin 1 was 6.6% and those of exfoliative toxins A and B were 4.1 and 1.5%. The total detection rate of toxins was 80.1% from 196 *S. aureus* strains (table 2) [2].

Neurological Examinations

Twenty (31%) of the 65 AD patients had at least one neurological subjective symptom. Neurological examina-

Table 2. Toxins detected by PCR from *S. aureus* obtained from skin lesions (n = 196)

<i>Detection rate, %</i>	
Total	80.1 (157/196)
SEA	9.7
SEB	55.6
SEC	7.7
SEE	30.6
TSST-1	6.6
ETA	4.1
ETB	1.5
<i>Toxins found in lesions, n</i>	
SEA	7
SEB	59
SEC	2
SEE	16
SEA, SEB	9
SEA, SEE	1
SEA, TSST-1	1
SEA, SEB, SEE	1
SEB, SEC, SEE	3
SEB, SEC, SEE, TSST-1	1
SEB, SEC, TSST-1	1
SEB, SEE	33
SEB, SEC, ETA	1
SEC, SEE	2
TSST-1 only	5
TSST-1, SEC	5
ETA	6
SEE, ETA	1
SEE, ETB	1
SEB, ETB	1
SEE, ETB	1
None	39
Total	196

SEs = Staphylococcal enterotoxins (A, B, C, E); TSST-1 = toxic shock syndrome toxin 1; ETA, ETB = exfoliative toxin A, B. Toxins such as SEs, TSST-1 and ETA/B were detected from as many as 80.1% of the strains. When SEA and SEB are combined, the detection rate was 60.2%.

tions showed at least one abnormal finding in 47 (72%) of the 65 AD patients. The frequency of neurological signs and symptoms in children with AD was basically equal to that in adult patients (table 3).

Magnetic resonance imaging (MRI) showed intervertebral disk degeneration in 32 patients (86%), disk bulging/protrusion in 29 patients (78%), posterior spondylo-

Table 3. Neurological symptoms and signs in children and adults with AD [3]

	Total AD (n = 65)	Child AD (n = 16)
Age (mean $\pm$ SD), years	25 $\pm$ 9	12 $\pm$ 2
Men	31 (48)	7 (44)
Neurological subjective symptoms	20 (31)	2 (13)
Neck/shoulder stiffness	14 (22)	2 (13)
Numbness/paresthesia in limbs	9 (14)	1 (6)
Muscle weakness in limbs	4 (6)	0 (0)
Urinary urgency	4 (6)	0 (0)
Neurological signs	47 (72)	13 (81)
Abnormal tendon reflexes	39 (60)	12 (75)
Hyperreflexia in legs	29 (45)	8 (50)
Finger jerks	34 (52)	10 (62)
Inverted radial jerks	15 (23)	4 (25)
Sensory disturbances	22 (34)	6 (38)
Decreased deep sensations	19 (29)	6 (38)
Decreased superficial sensations	13 (20)	4 (25)
Motor disturbances	15 (23)	4 (25)
Muscle weakness in legs	13 (20)	4 (25)
Muscle weakness in arms	4 (6)	1 (6)
Babinski sign	3 (5)	1 (6)

Values are numbers of patients, with percentages in parentheses.

listhesis in 24 patients (65%), kyphosis in 11 patients (30%) and thickening of yellow ligaments in 2 patients (5%), according to assessment by a neurologist. MRI findings were double checked by two neurologists, and there was no significant observer difference. The frequency of MRI abnormalities in children with AD was not different from the group of all AD patients.

Of the 12 normal controls (NC), MRI abnormalities were found in 9 patients (75%). The frequencies of intervertebral disk degeneration and posterior spondylolisthesis in the AD patients were significantly higher than in NC ($p < 0.05$, $p < 0.001$, respectively). Although the frequency of posterior spondylolisthesis in the multiple sclerosis (MS) patients was higher than in NC ($p < 0.005$), the frequencies of other findings in MS patients were nearly the same as in NC (table 4) [3]. Moreover, we experienced new patients with AD and neurological examinations revealed abnormalities in 59 out of 81 AD patients. Cervical MRI was performed in 46 patients randomly and showed abnormal findings in 38 of these patients.

Duodenal Biopsy Findings

We previously reported the findings of duodenal biopsy in 35 AD patients performed before May 2003. All cases

Table 4. Cervical MRI findings in patients with AD, MS and in NC [3]

	Total AD (n = 37)	Child AD (n = 9)	MS (n = 26)	NC (n = 12)
Age (mean $\pm$ SD), years	25 $\pm$ 8	13 $\pm$ 1	31 $\pm$ 8	23 $\pm$ 9
Men, %	46	44	19	58
MRI abnormalities, %	92, 89	100, 100	77, 73	75, 75
Intervertebral disk degeneration	86 ^{b, c} , 83 ^b	89 ^a , 89 ^a	50, 50	58, 58
Intervertebral disk protrusion	78 ^a , 78 ^a	100 ^a , 89	54, 50	67, 67
Mild	51, 54	56, 56	46, 42	58, 67
Moderate	27, 24	44, 33	8, 8	8, 0
Posterior spondylolisthesis	65 ^c , 65 ^c	78 ^d , 78 ^d	65 ^d , 65 ^d	8, 8
Mild	41 ^c , 41 ^c	44, 33	58 ^d , 58 ^d	8, 8
Moderate	24, 24	33, 44	8, 8	0, 0
Kyphosis of vertebrae	30, 30	22, 22	42, 42	33, 33
Thickening of yellow ligaments	5, 5	0, 0	0, 0	0, 0
Compression of cervical cord	24, 24	0, 0	8, 8	8, 8
Mild	22, 22	0, 0	8, 8	8, 8
Moderate	3, 3	0, 0	0, 0	0, 0
Abnormal lesion within the cord	3, 3	0, 0		0, 0

Values are percentages of patients assessed by two readers (left: reader No. 1, right: reader No. 2).

^a $p < 0.05$, ^b $p < 0.005$: differs from MS; ^c $p < 0.05$, ^d $p < 0.005$, ^e $p < 0.001$: differs from NC.

had abnormal findings in duodenal tissues, namely duodenitis [4]. With an increase in inflammatory cells in the lamina propria such as lymphocytes, plasma cells and sometimes eosinophils, the villi of the duodenum were noted to be short and stubby. In some cases, fibrosis of the lamina propria and the presence of lymphoid follicle formation, often associated with reactive germinal centers, were also noted. Those findings were considered to be compatible with chronic duodenitis. Apparently the duodenitis improved after the treatment. Serial duodenal biopsy tests were performed in 10 patients with AD. Chronic duodenitis disappeared after the disinfectant treatment combined with topical steroid in 5 patients (fig. 1, table 5).

Case Reports

(a) Figure 2 shows rapid improvements of skin rashes during this treatment. Levels of antitoxin IgE antibodies are elevated in AD, and the antibody titer correlated with the severity of skin lesions. Anti-SEA and anti-SEB IgE antibody titers and IgE levels were improved drastically in parallel during the treatment. In this case, the levels of anti-SEA antibody and anti-SEB antibody were normalized by the therapy.

(b) Figure 3 shows rapid improvement of skin rash and anti-SEB IgE antibody titers, and IgE levels also improved rapidly. SEB was detected from his *S. aureus*. No anti-SEA IgE antibody titer was detected.

Table 5. Results of total IgE, eosinophils in blood, endoscopic findings and histological diagnosis [4]

Case	Sex	IgE IU/ml	Eosinophils n/mm ³	Endoscopic findings	Histological diagnosis
1	F	23,940	360	small bleedings	chronic duodenitis
2	F	227	511	–	chronic duodenitis
3	F	23,342	1,196	small bleedings	chronic duodenitis
4	M	17,121	357	–	moderate duodenitis
5	F	9,200	533	–	mild duodenitis
6	F	4,024	623	–	mild duodenitis
7	F	21,212	722	–	mild duodenitis
8	F	11,829	258	–	mild duodenitis
9	F	17,968	339	–	duodenitis
10	M	2,661	280	–	chronic duodenitis
11	F	6,138	675	–	chronic duodenitis
12	M	4,417	265	–	chronic duodenitis
13	M	58,066	950	–	chronic duodenitis
14	M	14,480	950	–	chronic duodenitis
15	M	15,413	233	–	mild duodenitis
16	F	8,414	976	–	chronic duodenitis
17	F	3,866	3,330	–	chronic duodenitis
18	M	15,408	1,599	small erosions	chronic duodenitis
19	F	38,064	1,078	–	chronic duodenitis
20	M	39,802	594	–	chronic duodenitis
21	M	11,784	403	–	chronic duodenitis
22	F	48	228	–	chronic duodenitis
23	M	32,586	378	small erosions	mild duodenitis
24	M	10,852	199	–	mild duodenitis
25	F	9,348	51	–	mild duodenitis
26	F	3,849	210	–	mild duodenitis
27	F	9,526	441	–	mild duodenitis
28	M	18,388	1,360	–	mild duodenitis
29	M	3,471	989	–	chronic duodenitis
30	M	3,452	525	–	mild duodenitis
31	F	270	449	–	mild duodenitis
32	F	8,236	1,200	–	chronic duodenitis
33	F	1,262	304	–	mild duodenitis
34	F	2,070	700	–	mild duodenitis
35	M	6,353	448	–	mild duodenitis

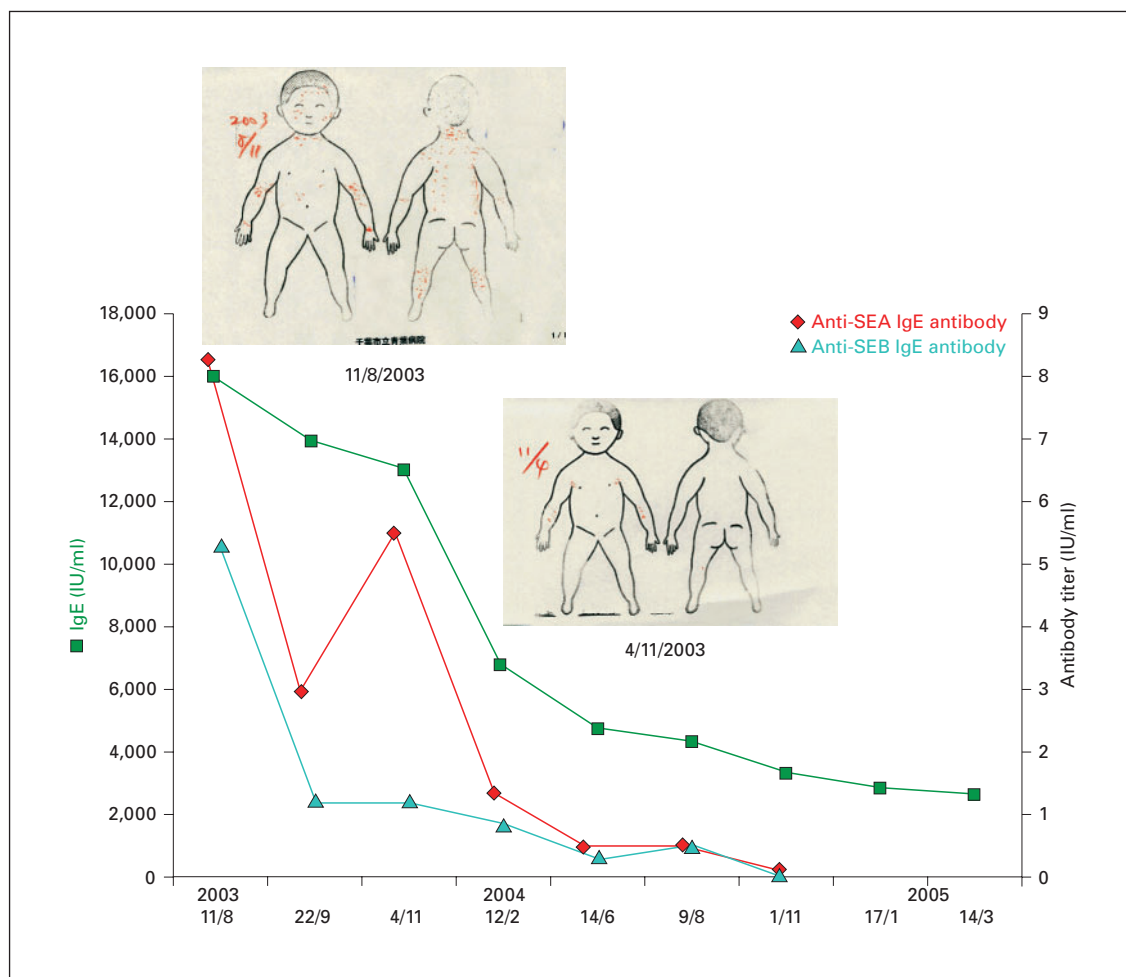


Fig. 1. Case 1 (19 years old, male). Changes in total IgE and anti-toxin IgE antibodies.

(c) Figure 4 shows rapid improvement of skin rash graphically, and rapid improvement of allergic tests was recognized. SEA and SEB were detected from her *S. aureus*. Her duodenum showed no significant change. Her cervical MRI showed cervical spondylosis.

(d) Figure 5 shows 1 patient with AD who had chronic duodenitis and cervical disk herniation. In this case, allergic tests resulted in similar improvements in a short period of time. And this case was our first with normalized duodenal tissues after therapy.

Duodenal Findings and Neurological Findings

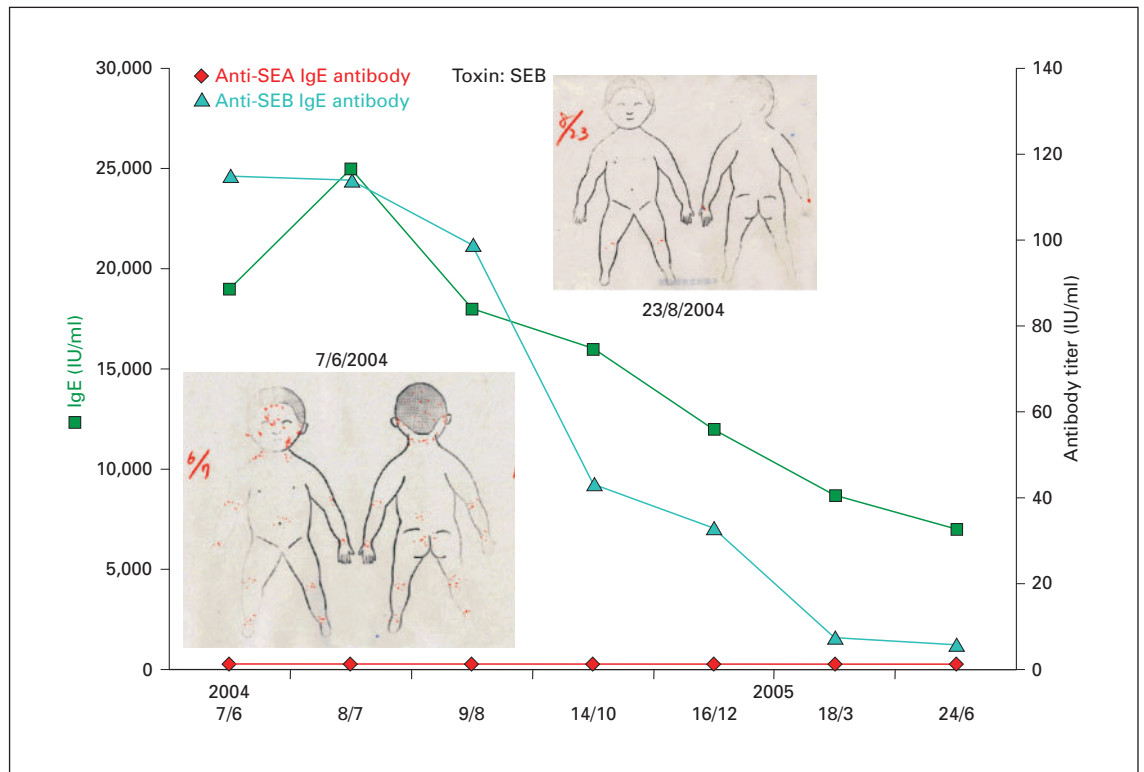
As shown in the summary of 23 AD patients who underwent neurological examination and duodenal biopsy, 7 showed no abnormal findings in cervical MRI and 2 pa-

tients showed normal duodenal tissue, but the other 14 AD patients showed abnormal findings both in cervical MRI and duodenal tissues. Eighteen patients showed abnormal findings both on neurological examination and in duodenal biopsy (table 6).

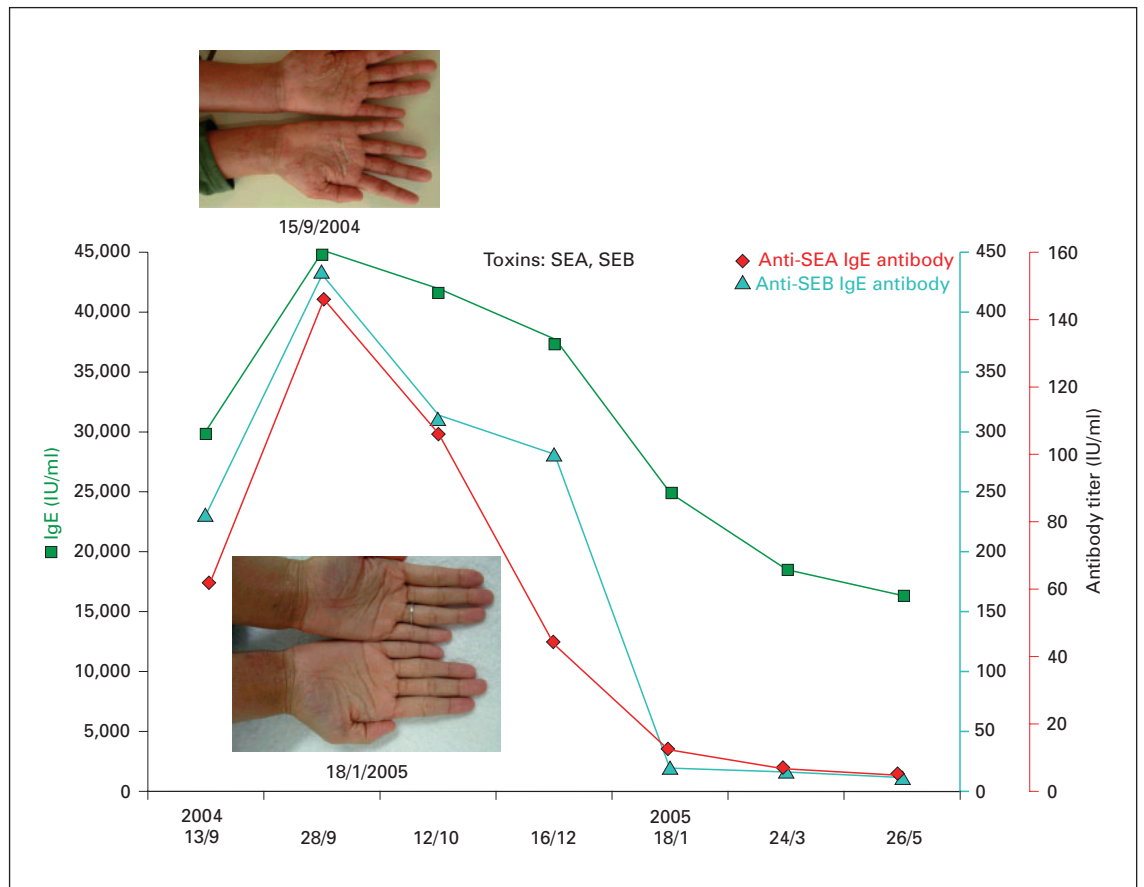
Fig. 2. Case 2 (4 years old, male). Changes in total IgE and anti-toxin IgE antibodies.

Fig. 3. Case 3 (28 years old, female). Changes in total IgE and anti-toxin IgE antibodies.

2



3



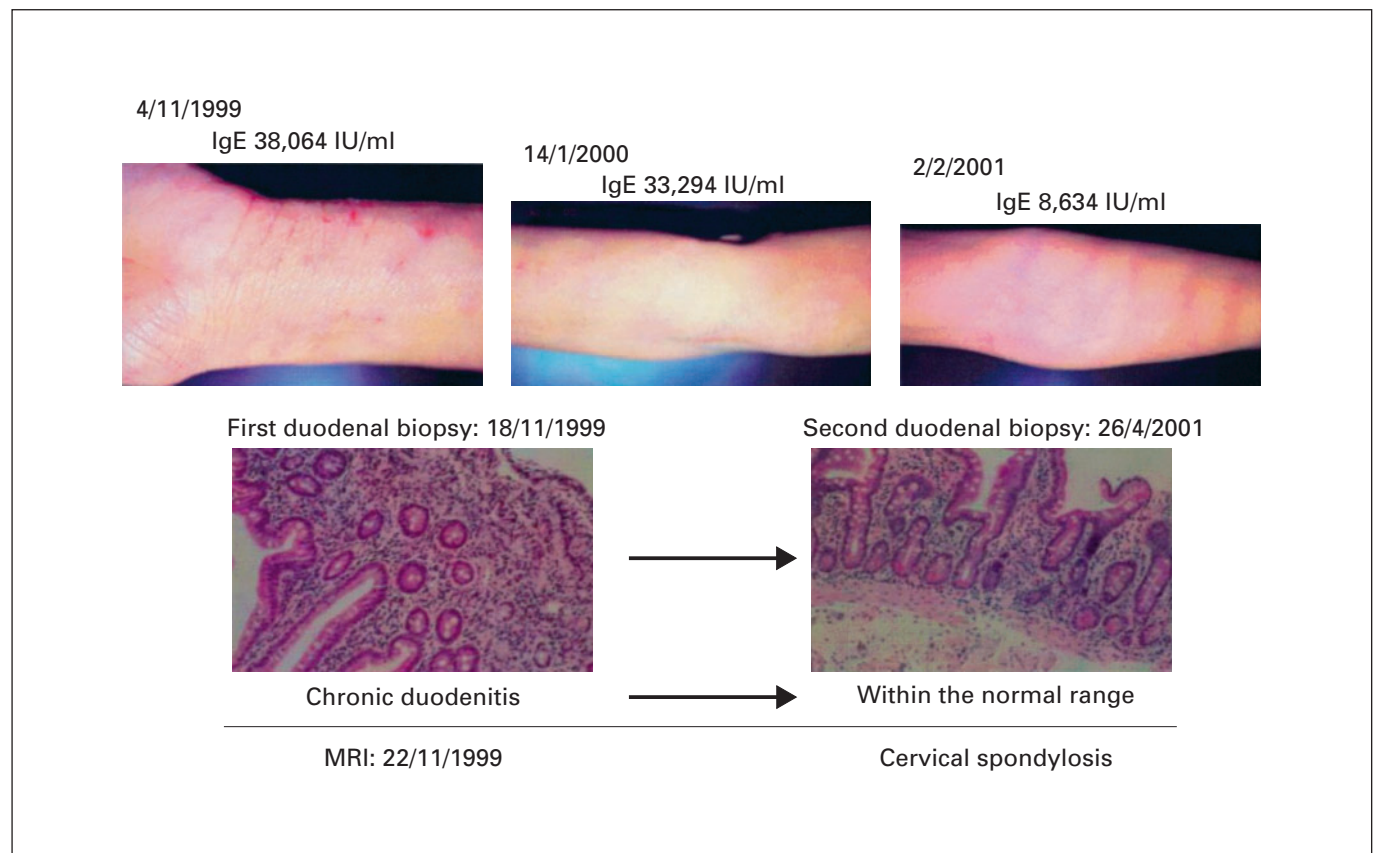
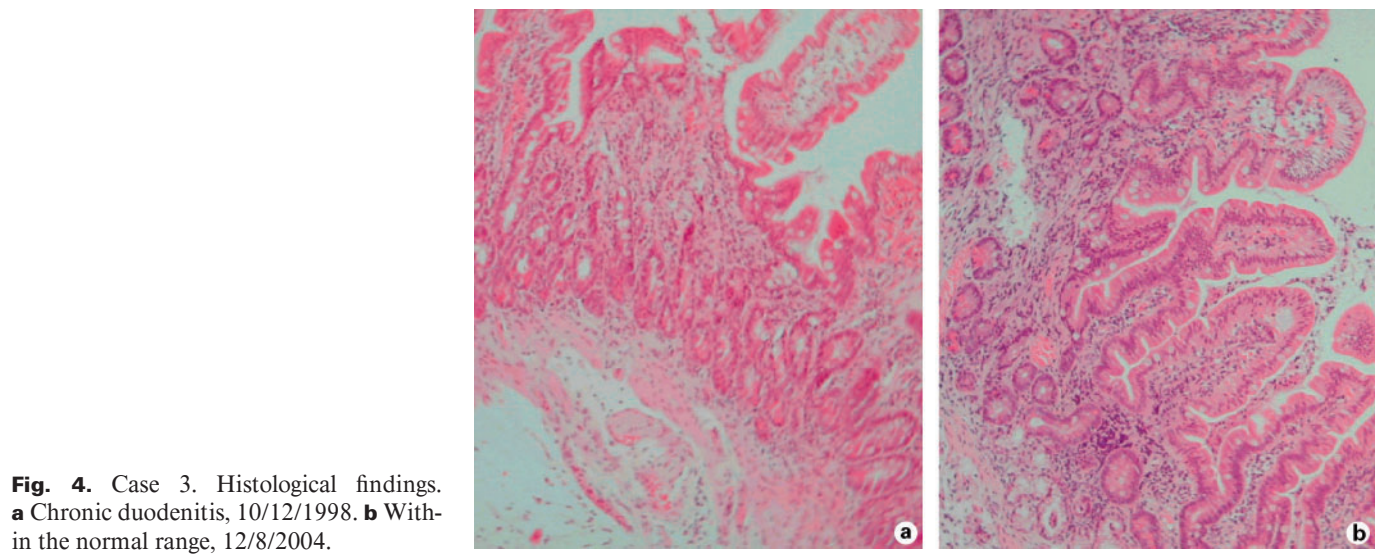


Fig. 5. Representative case of simultaneous improvement of skin and intestinal lesions by disinfection therapy in an AD patient.

Table 6. Duodenal biopsy and cervical MRI findings

Case	Age years	Histological diagnosis	Cervical MRI diagnosis	Clinical diagnosis
1	43	chronic duodenitis	CS, OYL	CM
2	32	chronic duodenitis	CS	CM
3	31	chronic duodenitis	CS	CM
4	26	chronic duodenitis	WNR	CM
5	21	chronic duodenitis	WNR	CM
6	23	chronic duodenitis		WNR
7	25	chronic duodenitis	CS	CM
8	28	mild duodenitis	CS	CM
9	24	chronic duodenitis	WNR	CM
10	36	chronic duodenitis	CS	CM
11	33	duodenitis	WNR	CM
12	24	mild duodenitis	CS	CM
13	29	chronic duodenitis	CS	CM
14	28	duodenitis	CS	CM
15	26	duodenitis	WNR	WNR
16	24	mild duodenitis	CS	CM
17	28	mild duodenitis	CS	CM
18	20	chronic duodenitis		WNR
19	26	chronic duodenitis	CS	CM
20	21	chronic duodenitis	CS	CM
21	32	WNR	CS	CM
22	28	WNR	CS	CM
23	24	chronic duodenitis	CS	CM

CM = Cervical myelopathy; CS = cervical spondylosis; OYL = ossification of yellow ligament; WNR = within normal range.

Summary and Discussion

AD is considered to be not a simple skin disease, but a systemic disorder involving multiple systems, from the demonstration of chronic inflammation of the large intestine by Yamada et al. [5] and the report by Kira et al. [6] of atopic myelitis in AD patients with hyper-IgE-emia. AD is associated with intestinal and cervical lesions [7, 8]. *S. aureus* has been suggested to contribute to the exacerbation of AD. *S. aureus* produces many kinds of toxins, which may be involved in the exacerbation of AD [9–12]. The toxin produced by *S. aureus* is called bacterial superantigen [13, 14]. Superantigens are capable of activating a large number of T cells (up to 30% of all T cells) without prior antigen processing. Therefore they differ from regular (nominal) antigens, which need processing by antigen-presenting cells and activate only specific (clonotypic) T cells (usually less than 0.1% of all T cells) [15]. And antitoxin IgE antibodies have been detected in AD patients in many reports [16–21]. Levels

of antitoxin IgE antibodies are elevated in AD and the antibody titer correlated with the severity of skin lesions.

We experienced numbers of cases with even severe skin rashes who showed dramatic improvement in a short period of time with therapy. AD is a common allergic disease and can be complicated by various medical conditions. Recently, Kira et al. [6] have reported acute myelitis associated with AD and hyper-IgE-emia, and they named the disease ‘atopic myelitis’. However, the frequency of myelitis in AD patients and the pathogenesis of atopic myelitis remain unclear. AD patients frequently showed neurological abnormalities such as abnormal tendon reflexes, mild sensory disturbances and mild motor disturbances. The MRI scans, however, rarely showed abnormal lesions within the cervical cord; instead, they showed evidence of intervertebral disk degeneration. Therefore, the neurological abnormalities in our AD patients might be due to cervical spondylosis rather than cervical myelitis. Ito et al. [3] reported that intervertebral disk degeneration was found more frequently in AD patients than in MS patients, so it is possible that Th2 dominant inflammation contributes to disk degeneration in AD patients. In conclusion, AD may be a risk factor for intervertebral disk degeneration [3]. Yamada et al. [5] have already demonstrated chronic large intestinal inflammation in AD patients by biopsy. We showed a high frequency of duodenitis in AD patients. AD is associated with intestinal and cervical lesions. *S. aureus* is frequently found on the skin of AD patients. Many patients experienced rapid improvement on levels in antitoxin IgE antibodies during the therapy. The eradication of bacterial superantigens might trigger improvement of the skin rash. Moreover, we observed that some AD patients who had duodenitis also had low serum IgE levels. Serial duodenal biopsy tests were performed in 10 patients. Chronic duodenitis disappeared after the disinfectant treatment combined with topical steroid in 5 AD patients.

The presence of bacterial superantigens might generate duodenitis and cervical disk degeneration. Our data clearly indicate that the combination therapy of disinfection and topical steroid is effective not only for the skin lesions, but gastrointestinal tract lesions and spinal complications, by eradicating bacterial superantigens.

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