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Case Report

Efficacy of Long-Term Sulfamethoxazole-Trimethoprim Therapy in a Boy with Hyperimmunoglobulin E Syndrome

Hiroshi Tanaka, Ryosuke Ito, Norio Onodera and Shinobu Waga[1]

Division of Pediatrics, Iwate Prefectural Kitakami Hospital, Kitakami 024-0063 and [1]Department of Pediatrics, Hirosaki University School of Medicine, Hirosaki 036-8562

Tanaka, H., Ito, R., Onodera, N. and Waga, S. *Efficacy of Long-Term Sulfamethoxazole-Trimethoprim Therapy in a Boy with Hyperimmunoglobulin E Syndrome.* Tohoku J. Exp. Med., 1998, **186** (1), 61–66 —— A boy with hyperimmunoglobulin E syndrome (HIE syndrome), who was successfully treated with long-term sulfamethoxazole-trimethoprim (SMX-TMP) is reported. He had been suffering from recurrent pruritic dermatitis soon after birth and had a significant high level of serum immunoglobulin E. Although an initiation of SMX-TMP therapy resulted in resolution of his clinical manifestations, cessation of the treatment exacerbated the symptoms. Chemoprophylaxis of other oral antibiotics, which were suitable for *Staphylococcus aureus* isolated from lesions of the patient were unsuccessful. Another trial of low-dose SMX-TMP therapy resulted in gradual subsidence of the clinical manifestations. From these observations, efficacy of SMX-TMP therapy to prevent bacterial infection in the patient is clinically apparent. Although precise mechanism of the therapy remains speculative, long-term SMX-TMP therapy might be of benefit and low clinical toxicity in HIE syndrome. —— hyperimmunoglobulin E syndrome; long-term use; low-dose trial; sulfamethoxazole-trimethoprim

The hyperimmunoglobulin E syndrome (HIE syndrome) is known as an immunological disorder, characterized by increased serum level of immunoglobulin E (IgE), recurrent infections and chronic eczematoid dermatitis (Soderberg-Warner et al. 1983; Yanagi and Tsuji 1985; Yokota et al. 1990). It has been reported that increase in production of IL-4, defective production of IFN-γ and impaired chemotaxis of polymorphonuclear leukocytes (PMNs) in the syndrome (Soderberg-Warner et al. 1983; Yokota et al. 1990; Wilson et al. 1993).

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Address for reprints: Hiroshi Tanaka, M.D., Division of Pediatrics, Iwate Prefectural Kitakami Hospital, 3-15-36 Kunen-bashi, Kitakami-shi, Iwate 024-0063, Japan.

However, precise pathogenesis of the disease remains to be elucidated.

Although no curative treatment of HIE syndrome has been seen, efficacy of prophylactic sulfamethoxazole-trimethoprim (SMX-TMP) therapy on managing clinical problems and preventing bacterial infections were reported (Hattori et al. 1993; Honda et al. 1996). We describe here a boy with probable HIE syndrome who showed an evidence of clinical improvement following long-term SMX-TMP therapy. Judging from the clinical course, in which each cessation of the treatment exacerbated cutaneous lesions and bacterial infections in the patient, efficacy of SMX-TMP therapy was confirmed.

Case Report

A 5-month-old boy, whose parents were unrelated, referred to our hospital because of eczematoid dermatitis with cutaneous abscesses on the face and the scalp. He had been suffering from recurrent pruritic dermatitis since a week after birth. Except for the cutaneous lesions, he was quite well. Family history was negative for susceptibility to infection nor allergic disorders. *Staphylococcus aureus* (*S. aureus*) was isolated from abscesses on the scalp. His white blood cell (WBC) counts increased at 28.3×10^9/liter with marked eosinophils of 32%. The serum level of IgE showed a significant increase for his age (680 IU/ml, by radioimmunosorbent test). Although anti-*S. aureus* IgE antibody was not detected by radioallergosorbent test (RAST), a positive allergic reaction for egg was detected. After a tentative diagnosis of atopic dermatitis (AD) with impetigo had been made, oral ketotifen (Zaditen®, Novartis Co., Basel, Swiss) accompanied with gentamicin/betamethasone ointment therapy was started. His cutaneous lesions were persistent with waxing and waning under the therapy and absesses were drained surgically. At the age of 7 months, his serum level of IgE increased to 2300 IU/ml. Therefore chemoprophylaxis of oral cefaclor was commenced for his superficial infection, but it was unsuccesful. Since *S. aureus* was still isolated from the abscesses and found to be susceptible to SMX-TMP, SMX-TMP (SMX 40 mg/kg/day, TMP 8 mg/kg/day) therapy was started at the age of 9 months. Thereafter his cutaneous lesions and eosinophilia gradually subsided. The serum level of IgE also decreased to 840 IU/ml. Thus SMX-TMP was discontinued after 3-month course and followed by oral ketotifen. His laboratory data at the age of a year were as follows: WBC, 10.3×10^9/liter with 9% neutophils, 90% lymphocytes and 1% eosinophils; hemoglobin, 121 g/liter; platelets, 217×10^9/liter; total protein, 70 g/liter; IgG, 17.2 mg/ml; IgA, 0.5 mg/ml; IgM, 2.8 mg/ml; IgE, 590 IU/ml; C3, 0.9 mg/ml; C4, 0.7 mg/ml and hemolytic complements activity, 30.0 U/ml. The other blood chemistry findings were unremarkable. The results of immunological studies are depicted in Table 1. Although chemotaxis of PMNs was not examined, phagocytosis and hydrogen peroxide production measured by flow cytometry (Hasui et al. 1989) at Special Reference Laboratories Inc. (Tokyo), showed normal values of 80% (normal values, 70–90%) and 79% (nor-

TABLE 1. *Summary of immunological studies of the patient at the age of a year*

IgG subclasses		Lymphocyte proliferation	
IgG1	11.3 mg/ml, 71.5% (60.5-88.3%)	phytohemaggulinin	255618 cpm (control 706.1 cpm)
IgG2	3.9 mg/ml, 24.5% (9.3-30.5%)		
IgG3	0.35 mg/ml, 2.2% (3.0-11.9%)	concanavalin A	115015 cpm (control 262 cpm)
IgG4	0.25 mg/ml, 1.6% (0-12.1%)		
Lymphocyte populations		Lymphokines	
T cell	78.6% (62.5-78.9)	IL-2	7.2 U/ml (RIA, 4-25)
B cell	16.8% (5.1-21.5)	IFN-γ	<6 U/ml
Null cell	4.4% (4.1-22.6)	(50% neutral red uptake method)	
CD4	55.1% (30.5-53.7)	Functional antibodies	
CD8	17.0% (17.4-43.0)	measles	(+)
CD3	74.5% (58.6-89.0)	Delayed skin test	
CD4/CD8	3.2% (0.5-2.3)	dinitrochlorobenzene	(+)

Data in parenthesis indicate the normal values; Values in parenthesis of IgG subclasses are normal ranges for a year described by Hayashibara et al. (1993)

mal values, $>70\%$), respectively.

Since his cutaneous lesions had been worsened after 2 months from the cessation of SMX-TMP, a trial of low-dose SMX-TMP therapy (SMX 20 mg/kg/day, TMP 4 mg/kg/day), partly because to avoid clinical toxicity, was started and which resulted in improvement of the lesions. Although his serum level of IgE gradually increased at 11 240 IU/ml with positive allergic reaction for egg white and *Candida albicans* by RAST by the age of 4 years, he was well under the therapy except for mild eczematoid rash on the face and the neck. Because of long-term use and favorable clinical course, SMX-TMP was discontinued at the age of 5 years when he experienced bone fracture of the right foot by an accident, and followed by anti-histamines and oxatomide (Celtect®, Kyowa Hakko Co., Tokyo).

A month later from the cessation of SMX-TMP, recurrent cervical lymphoadenitis and pneumonia, which were caused by *S. aureus*, *Streptcoccus pneumonia* and *Hemophilus infuluenzae* occured. Although each infectious episodes were successfully treated with intravenous antibiotics, oral prophylactic cefaclor, erythromycin or fosfomycin were unsuccesful. When methicillin-resistant *S. aureus* (MRSA) was isolated from the cutaneous lesions, the need to use oral minocycline and vancomycin-conjugated ointment for further treatment occurred. Thus another trial of low-dose SMX-TMP (SMX 10 mg/kg/day, TMP 2 mg/kg/day) was started at the age of 6 years, and which resulted in gradual subsidence of the cutaneous lesions, cervical lymphoadenitis and pneumonia. During the long-term SMX-TMP therapy, no serious clinical toxicity was seen. At the age of 8 years, he is quite well and his growth velocity seems to be within

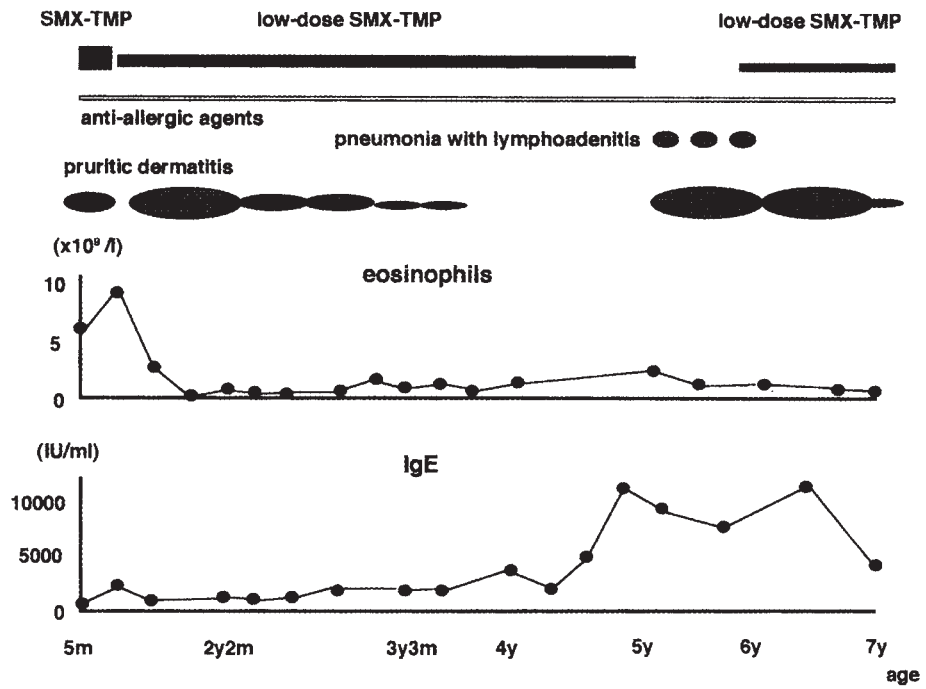

Fig. 1. Clinical course of the patient. Serum IgE and eosinophils fluctuated. Although the initiation of SMX-TMP accompanied with anti-allergic agents seemed to suppress the initial eosinophilia, the level of serum IgE fluctuated independently. Each cessation of SMX-TMP therapy exacerbated clinical symptoms.

normal range.

His serum levels of IgE and eosinophils fluctuated during the clinical course. These changes are shown in Fig. 1.

Discussion

The present case described here showed a persistent pruritic dermatitis soon after birth, and had a significant increase of serum IgE with recurrent episodes of cutaneous abscesses, cervical lymphoadenitis and pneumonia. These clinical manifestations were compatible with the character of HIE syndrome (Soderberg-Warner et al. 1983; Yanagi and Tsuji 1985; Yokota et al. 1990). Although immunological studies for HIE syndrome in the present patient were not sufficient, his clinical course indicated that he has probable HIE syndrome rather than simple AD.

To date, therapeutic strategies in HIE syndrome have not been established. Therefore, treatment of the syndrome is based on clinical findings and mainly preventing bacterial infections. Jeppson et al. (1991) reported that recombinant IFN-γ enhances chemotaxis of PMNs in vitro in patients with HIE syndrome. However, the clinical efficacy of recombinant IFN-γ therapy in patients with HIE syndrome has not been established. Recently, a beneficial effect of SMX-TMP therapy in patients with chronic granulomatosis (Kobayashi et al. 1978), Wegener's granulomatosis (Imai et al. 1994) and HIE syndrome (Hattori et al.

1993; Honda et al. 1996) have been reported. Concerning HIE syndrome, Hattori et al. (1993) reported the beneficial effect of SMX-TMP therapy, which was associated with a transient recovery of impaired chemotaxis of PMNs, but without enhancing effects on hydrogen peroxide production and phagocytosis in a 13-year-old boy with the syndrome. Honda et al. (1996) reported that a 34-year-old woman with the syndrome, who had been suffering from recurrent respiratory infections caused by MRSA was successfully treated with SMX-TMP. From these reports as in ours, the efficacy of SMX-TMP therapy in HIE syndrome are clinically apparent. However, the precise mechanism of SMX-TMP in the syndrome remains speculative, since in vitro studies did not consistently demonstrate the beneficial effects of SMX-TMP (Hattori et al. 1993).

Another interesting finding in our patient is that the efficacy of low-dose SMX-TMP therapy was observed. Although *S. aureus* except for MRSA isolated from the lesions was susceptible to SMX-TMP, a significant bactericidal effect of the low-dose therapy was uncertain. Moreover, the lesions caused by MRSA gradually subsided under SMX-TMP therapy as in the previous report (Honda et al. 1996). In the present case, a favorable clinical course may not indicate the effectivness of SMX-TMP therapy, since natural course of the disease is not excluded. However, his clinical course, in which each cessation of SMX-TMP exacerbated clinical symptoms, suggests a beneficial effect of SMX-TMP therapy in the clinical improvement.

In conclusion, low-term low-dose SMX-TMP therapy might be of benefit and low clinical toxicity to prevent bacterial infections in patients with HIE syndrome. However, precise mechanism of the SMX-TMP therapy remains speculative. Further studies will be neccessary.

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