0031-3998/86/2007-0685$02.00/0
PEDIATRIC RESEARCH

Vol. 20, No. 7, 1986
Printed in U.S.A.

Transient Remission after Intercurrent Measles Infection in a Patient with Hyperimmunoglobulin E Syndrome

CHING-YUANG LIN

The Pediatric Research Laboratory, Department of Medical Research and Pediatrics, Veterans General Hospital Hospital, Taiwan, Republic of China

ABSTRACT. A 5-yr-old patient with hyper IgE syndrome contracted measles. This was accompanied by a temporary disappearance of his skin lesions. The patient had a long history of recurrent infections, chronic eczematoid pruritic dermatitis, and elevation of serum IgE level since infancy. Immunologic studies revealed decreased suppressor T cells (OKT8 cells) with increased IKT4/OKT8 ratio, defect in suppressor T cell function, and decreased chemotactic index. In February 1985, when he developed an interrcurrent measles infection at age of 5, the eczematoid pruritic dermatitis disappeared completely and immunologic defects improved transiently, with normalization of OKT4/OKT8 ratio, decrease in *in vitro* IgE synthesis, *in vivo* serum IgE level, and interleukin-2 production, decreases in IgG Fc receptor-bearing cells and autologous mixed lymphocyte reaction, and normalization of chemotactic index. One month later, the eczematoid skin lesion relapsed and immunologic defects reappeared. These studies suggested that the pathogenesis of hyper IgE syndrome involved a hypofunction of suppressor T cell. The transient remission associated with measles infection is probably related to the effect of the virus on the helper T cells, resulting in a normalization of OKT4/OKT8 ratio and IgE production. (*Pediatr Res* 20: 685–688, 1986)

Abbreviation

IL-2, interleukin-2

The hyper IgE syndrome is characterized by recurrent staphylococcal abscesses of the skin, lungs, joints, and other sites, beginning in infancy; blood and tissue eosinophilia; and extremely elevated serum IgE concentration (1–5). Although all patients have had a pruritic dermatitis at some time in their lives, the distribution of the lesions is not typical for atopic dermatitis, and the respiratory allergic symptoms are usually absent (1, 4). The pathogenesis of this disease is unknown, but abnormal regulatory T cell functions (1, 2), defect of suppressor T cell function (6), and defect in *in vivo* and sometimes *in vitro* neutrophil chemotaxis (5) have been reported.

Natural measles infection can cause prolonged depression of cell-mediated immunity and induce remission of steroid-sensitive nephrotic syndrome (7–9). This has been attributed to the effects of measles virus on the immunologic system (7, 9). However, to our knowledge, a transient remission after measles infection in patients with hyper IgE syndrome has not been reported. Therefore, we thought it worthwhile to report our experience with one patient with hyper IgE syndrome who experienced transient, but complete remission of the skin lesion, and dramatic improvement in immunologic abnormalities after intercurrent measles infection. In an attempt to elucidate the pathogenesis of hyper IgE syndrome and immunologic changes after measles infection, we measured T cell subpopulations, lymphoproliferative response, autologous mixed lymphocyte reaction, *in vitro* IgE synthesis, and chemotaxis in remission and during relapse.

Received August 19, 1985; accepted January 23, 1986.
Address for correspondence Dr. Ching-Yuang Lin, Pediatric Research Laboratory, Department of Medical Research, Veterans General Hospital, Shih-Pai, Taipei, Taiwan, 11217, R.O.C.

MATERIALS AND METHODS

Total T lymphocytes (Total T cells) and B cells (fluorescent method) were prepared and detected according to the method of Kerman *et al.* (10) with slight modification (9). Phenotypic analysis of T cell subpopulations were analyzed by indirect immunofluorescence using mouse monoclonal antibodies (9) (OKT4, OKT8, and OKIal antisera; Ortho Pharmaceutical Corporation). The lymphocytes bearing IgG Fc receptors were detected according to the method of Thompson *et al.* (11) with rosette assay employing fixed ox erythrocytes coated with human IgG.

Lymphoproliferative responses to phytohemagglutinin and measles antigen were measured as previously described (9). Briefly, lymphocytes were separated with Ficoll-Hypaque density gradient and cultured in 1×10^6/ml of RPMI1640 on microtiter U plates containing 10% healthy control's AB serum and were calculated as count per minute.

Autologous mixed lymphocyte reaction was carried out as previously described (12). Briefly, 0.1 ml of T lymphocyte suspension was mixed with 0.1 ml of B cell and monocyte suspension and then cultured in round-bottom microtiter plates (Flow Laboratories) for 7 days in a humidified 5% CO_2, 37° C incubator. The B cells and monocytes were pretreated with 50 μg/ml of mitomycin C for 30 min at 37° C. Twenty h before the end of culture, 1 μCi H^3-thymidine (New England Nuclear, Boston, MA, specificity 6.7 Ci/mM) in 20 μl RPMI1640 was added to the cultures. The cells were harvested by an automatic harvester and the radioactivity was counted. Stimulation index was calculated by dividing the cpm of stimulated culture by that of unstimulated counterpart.

Complement-dependent lysis of T cell subsets was carried out using 20 million T lymphocytes suspended in 0.8 ml of a 1:250 dilution of anti-OKT8 or anti-OKT4 antibody in phosphate-buffered saline and incubated for 1 h at room temperature. Then 0.2 ml rabbit complement (Pel-Freeze Biological Inc, Rogers, AR) was added and the suspension was incubated for an additional 60 min at 37° C. Immunofluorescence of the lymphocytes before and after treatment with anti-OKT8 or anti-OKT4 anti-

body and complement demonstrated complete (> 98%) removal of the corresponding T cell subset from the cell suspension.

The effect of normal control cells on *in vitro* IgE synthesis by the patient's lymphocyte subsets was assessed by coculture technique. T lymphocytes were separated from mononuclear cells after Ficoll-Hypaque gradient by rosetting first with neuraminidase-treated sheep erythrocytes overnight in ice water and then centrifuging over Ficoll-Hypaque density gradient. The interphase cell which contained 40–47% sIg(+) lymphocytes were designated as B lymphocyte-enriched population. Normal control T8, T4 cells were match mixed with patient's T8, T4 cells in a 1:1 ratio and cultured at a concentration of 1×10^6 cells/ml in a final volume of 1 ml/culture. The value of IgE observed in the supernatant of mixed cell culture was measured at the end of the 6 day culture period by using Phadebas IgE PRIST Kits (Pharmacia, Sweden).

The production of interleukin-2 (IL-2) from patient's MNC was induced by the 1 μg/ml phytohemagglutinin and 5 ng/ml of phorbol myristic acetate (P8139, Sigma). After 48 h of incubation at 37° C and 7% CO_2, supernatant was collected by centrifugation. The cell line used to detect the presence of IL-2 was CTLL-2 (13).

The measurement of IL-2 receptor (Tac) was carried out by indirect immunofluorescence using monoclonal antibody before and after 3 days of measles antigen stimulation.

Delayed type hypersensitivity skin test to PPD was read after 48 h; and induration with diameter greater than 5 mm was considered positive.

The inhibition of macrophage migration was determined by employing indirect agarose method as described previously (9), measles antigen was employed in a concentrations of 0.02 ml of preservative-free stock solution per ml of phosphate buffer solution. Twenty healthy children who had a positive skin test to PPD and measles vaccination were selected as control.

The patient's macrophage and neutrophil chemotactic activities were performed as described by Ward (14) and others (12). The chemotactic index was calculated by the following formula:

$$\frac{\text{cells that migrated with C5 chemotactic fragment}}{\text{cells that migrated with medium}}$$

Briefly, measles virus (Edmonston strain B) was grown in Vero cells, purified by two cycles of sucrose gradient centrifugation at $100{,}000 \times g$ for 2 h. The supernatant was inactivated by heating at 56° C for 45 min and dialyzed against PBS to a final concentration of 200 μg protein/ml determined according to Lowry *et al.*

Ten normal, healthy, age- and sex-matched children were included in the control group.

CASE REPORT

A 5-yr-old Chinese boy had a long history of recurrent staphylococcal skin abscesses and eczematoid eruption since the 1st month of life. As an infant he developed recurrent sinusitis, pneumonia, and otitis media in February 1980. He was first admitted to a hospital with the chief problems of oral thrush, pneumonia, eczematoid lesions, and pustules over the extremities, face, and trunk. Skin cultures yielded coagulase-positive *Staphylococcus aureus* and oral scrapings grew *Candida albicans*, which responsed to oxacillin and nystatin, respectively. At age of 2 yr, he was afflicted with pneumatocele after recurrent staphylococcal pneumonia. At age of 3, he developed severe eczema herpeticum caused by herpes simplex type 1 infection requiring systemic acyclovir treatment. There was no adverse reaction observed following routine immunizations. His father had allergic rhinitis, but his mother and three sisters were healthy. Laboratory investigations revealed normal hemograms except for an intermittent eosinophilia which fluctuated between 15 and 30%. Quantitative Ig determination revealed mild elevation in IgG (1600 mg/dl), IgA (120 mg/dl), and IgM (130 mg/dl). The serum IgE ranged from 6,000 to 12,000 U/ml. Serum C3, C4, and CH_{50} were normal. The T cell, T cell subsets, cellular immunity studies, and chemotactic index are shown in table 1. Nitroblue tetrazolium test was 24% in unstimulated state. On February 2, 1985 he developed generalized eczematoid lesions and pustules over the face, trunk, and extremities (Fig 1*a*). He had come into contact with a measles patient on that day. One week later, he developed fever, conjunctivitis, and coryza. Two days later, the eczematoid lesions and pustules completely disappeared without any medication (Fig 1*b*), a situation which had never occurred during the past 5 yr). A maculopapular rash appeared from the head extending to the trunk and limbs. One week after this episode, the maculopapular rash disappeared with normal skin appearance (Fig 1*b*). However, eczematoid skin lesions with pustules developed again 1 month later.

Measles virus serology was performed before and after this episode and an increase in measles antibody titer (rising from 1:2 to 1:128 of complement-fixation antibody titer was detected), compatible with a recent measles infection. Blood chemistry including renal and liver functions remained within normal limits. The data of immunologic studies during this spontaneous remission of the long standing eczematoid skin lesions associated with measles infection and relapse are summarized in the Tables 1 and 2.

RESULTS

Immunologic profile. BCG vaccination is used for prophylaxis against tuberculous infection in our country. Delayed type hypersensitivity skin tests to PPD (1TU, 5TU, 200TU) were negative during acute measles infection, but became positive 1 month later.

The profiles of lymphocyte subsets, lymphoproliferative response, autologous mixed lymphocyte reaction, and lymphokine production studies in this patient during acute measles infection and relapse of skin lesion are as shown in Table 1. Total white cell count and absolute lymphocyte count decreased in number during the acute measles infection, but returned to the normal range 4 wk later. The same changes were noted also in the OKT4 cells, OKT8 cells, OKIal cells, total T and B cells. Whereas the OKT4/OKT8 ratio returned to normal range during measles infection, but decreased again 4 wk later. The IgG Fc receptor-bearing cells was within normal range, but increased again 4 wk later.

During the acute measles infection, lymphocyte proliferative response, IL-2 receptor and IL-2 production were significantly lower in lymphocytes cultured with either phytohemagglutinin or measles antigen. In the relapse of skin lesions, these returned to normal.

This was also true for leukocyte migration index to measles antigen during measles infection was 92%, higher than that (> 80%) of healthy controls. One month later, this index became normal.

In vitro synthesis of IgE. As shown in table 2, IgE production became normal (240 pg/culture) during the measles infection, but markedly increased (2600 pg/culture) 1 month later. When the patient's peripheral OKT8 cells were present in the coculture, a significantly increased IgE secretion was obtained. However, the patient's OKT4-enriched cells could not enhance IgE synthesis by the patient's B cell. During the measles infection the response did not differ from that of normal control. However, overproduction of IgE developed again in relapse of the skin lesions.

Serial determinations of *in vitro* neutrophil chemotaxis were performed, but the results were variable and the chemotactic defects did not correlate to the presence or absence of infection.

DISCUSSION

Janeway *et al.* (7), Blumberg and Cassady (8), and our group (15) have demonstrated spontaneous remission of nephrosis after

Table 1. *Immunologic parameters before, during, and in relapse after measles infection*

	Before measles infection	In remission during measles	In relapse after measles*	Controls ($n = 10$)
Absolute lymphocyte count (/mm^3)	3860	1366	4400	3414 ± 864/mm^3
Total T cell (/mm^3)	2316	614	2728	2642.2 ± 428.4/mm^3
OKT4 cell (/mm^3)	1737	491	2024	1702.6 ± 244.4/mm^3
OKT8 cell (/mm^3)	617	273	792	962.5 ± 262.4/mm^3
B cell (/mm^3)	501	109	528	866.4 ± 125.6/mm^3
OKIal cell (/mm^3)	656	40	660	526.4 ± 106.8/mm^3
Serum IgE (U/ml)	6,000–12,000	840	6700	<250
Lymphoproliferative response to				
Phytohemagglutinin (5 μg/ml) (Δcpm)	114724	69320	106617	122068 ± 47055
measles antigen (Δcpm)	ND†	44364	103214	104368 ± 32062
IL-2 production (U/ml)	ND	16.2	120.4	44.6 ± 4.4
IL-2 receptor (Tac) (with measles antigen)	ND	16%	67%	62.4 ± 8.6%
MIF (measles antigen)	ND	92%	70%	<80%
AMLR: T cell response to				
T (Δ cpm)	1410	15524	1777	9548 ± 3642
B cell (stimulation index)	0.17	1.22	0.33	1.84 ± 1.42
monocyte (stimulation index)	0.21	0.85	0.36	1.21 ± 0.42
Chemotaxis index	0.90	1.32	0.92	1.5 ± 0.2

* In relapse performed 2 months later after measles infection.
† Not done.

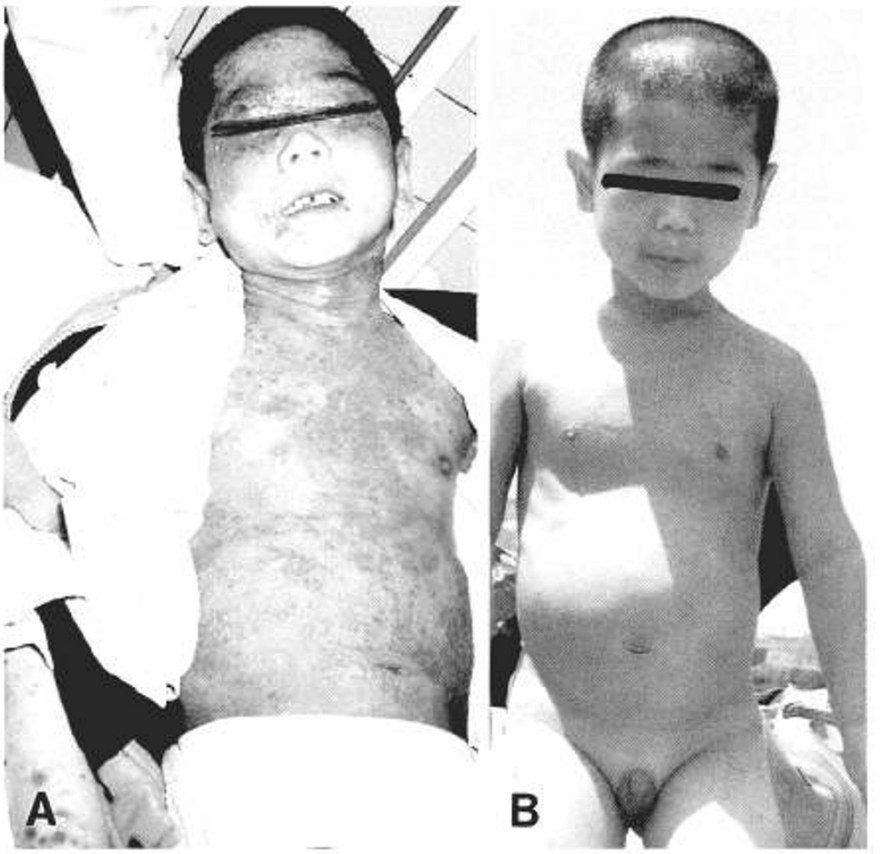

Fig. 1. *a,* the eczematoid lesions and pustules over face, trunk, and limbs were noted before measles infection. *b,* 10 days after contract with measles patient, his eczematoid lesions and pustules disappeared with some maculopapular measles' rash over the trunk.

intercurrent measles infection in children. The duration of the remission induced by measles varied from 1 to 7 months. However, there has been no report of transient improvement in both immunlogic and clinical features after measles infection in patients with hyper IgE syndrome. The mechanism of measles-induced remission is not clear, but the effects of measles virus on the immunologic system may play a role (15). Natural measles infection is known to cause prolonged depression of cell-me-

Table 2. *In vitro IgE synthesis in cocultures of patient and healthy control cells during acute measles and in relapse*

	In remission IgE (pg/culture)	In relapse IgE (pg/culture)
PT8 + PT4 + PB*	240	2600
PT8 + PT4 + NB	200	1600
NT8 + NT4 + NB	100	100
NT8 + NT4 + PB	110	120
PT8 + NT4 + PB	220	1400
PT4 + NT8 + PB	90	110

* P, patient; N, normal control; T8, OKT8 cells; T4, OKT4 cells: B, B cells.

diated immunity (15, 16), including a negative *in vitro* delayed type hypersensitivity skin test (16). The measles virus can also directly infect the lymphoid cells, as shown by the presence of measles virus in lymphocytes by immunofluorescence (17) and recovery of the virus (18) during the acute infection.

The immunologic defects that lead to the chronic infections and eczematoid lesion in the hyper IgE syndrome are not yet established. Geha *et al.* (6) suggest that a defect in number and function of suppressor T cells may be the primary factor in the regulation of IgE synthesis in the hyper IgE syndrome. In our case, the OKT8 cells were decreased both before and in relapse. However, OKT4 cells markedly decreased resulting in normalization of the OKT4/OKT8 ratio during acute measles, accompanied by a decreased serum IgE level and the disappearance of the eczematoid skin lesions. These findings were in accord with mouse experiments, in which measles virus infection affects predominantly the helper T lymphocytes and mildly the B lymphocytes (19).

The *in vitro* overproduction of IgE from patient's lymphocytes before measles infection and during relapse appeared to correlate with the change of OKT8 cells. The series of mixing experiments show that the *in vitro* IgE synthesis was significantly increased by patient's OKT8 cells in coculture. In contrast, patient's OKT4 cells did not enhance IgE secretion either by the B cells of the patient or normal group. These phenomena disappeared during acute measles infection. These results suggest that the decrease in OKT8 suppressor cells and increase in OKT4/OKT8 ratio are related to the elevation of serum IgE.

Another interesting finding in this hyper IgE syndrome patient was the autologous mixed lymphocyte reaction results. We have demonstrated that the T cells response to the stimulation of autologous non-T cells in this patient was lower than normals, but became normal during measles infection. However, the mechanism for this change is not clear.

In summary, the reason why measles infection can induce transient spontaneous remission of clinical features of hyper IgE syndrome is probably related to the effect of the virus on the helper T cells, resulting in a normalization of OKT4/OKT8 ratio and IgE production. These clinical and immunological observations will be helpful in understanding the overproduction of IgE in these patients.

Acknowledgments. The author thanks professor Michiaki Takahashi, Department of Virology, Osaka University, Osaka, Japan for the kindly gift of specific measles antigen and Dr. Thomas A. Waldman, Chief of Metabolism Branch, NCI for the kindly gift of anti-Tac antigen antibody.

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