Allergology International. 2008;57:99-105
DOI: 10.2332/allergolint.C-06-52

CASE REPORT

Selective IgM Deficiency Accompanied with IgG4 Deficiency, Dermal Complications and a Bronchial Polyp

Gen Ideura[1], Kazunaga Agematsu[2], Yoshimichi Komatsu[1], Orie Hatayama[1], Masanori Yasuo[1], Kenji Tsushima[1], Masayuki Hanaoka[1], Tomonobu Koizumi[1], Keisaku Fujimoto[1] and Keishi Kubo[1]

ABSTRACT

Background: IgM deficiency is a rare primary immunodeficiency. As few studies of selective IgM deficiency have been reported among the various other types of primary immunodeficiencies, the detailed pathogenesis of this disorder remains to be elucidated.

Case Summary: We clinically analyzed a 37-year-old woman who presented with IgM and IgG4 deficiency and ectopic bronchial pneumonia, and investigated immunological functions. Occlusive pneumonia was repeatedly observed in the right S6 area, and bronchoscopy revealed a polyp in the right B6 orifice, which was later identified as a fibroepithelial polyp after transbronchial endoscopic polypectomy. Two months later, pneumonia involving the right inferior lobe developed. Systemic erythema and pigmentation with bleb formation were also observed on the skin, and were thought to be drug-induced exanthema following a biopsy. Serum levels of IgM and IgG4 were extremely low at 3.0 mg/dl and less than 2.0 mg/dl, respectively. Circulating CD20 positive B cells were mildly reduced and memory B cells were markedly decreased. The majority of B cells expressed IgM on their surface. There were no abnormalities in cell counts of neutrophils, T cells, NK cells and monocytes. Chemotaxins, bactericidal activity and phagocytosis of neutrophils were normal.

Discussion: There have been no case reports of selective IgM deficiency with concurrent IgG4 deficiency, various dermal symptoms and a bronchial polyp, as demonstrated in our patient.

KEY WORDS

bronchial polyp, drug-induced exanthema, immunoglobulin G4 deficiency, selective immunoglobulin M deficiency

INTRODUCTION

Selective IgM deficiency has been associated with recurrent infections, and it has also been reported that many patients show increases in levels of other immunoglobulins, such as IgG, IgE and IgA in the presence of IgM deficiency or reduction.[1] In Japan, 8 men and 5 women were registered as having IgM deficiency according to statistical data collected by the Ministry of Health and Welfare in 2000.[2] Goldstein MF *et al*.[3] reported that the prevalence of selective IgM in adult populations was 0.26% and may be more common than previously thought. This disorder can be classified into 2 types: primary IgM deficiency represented by Wiskott-Aldrich syndrome and Bloom syndrome,[4] in which congenital IgM deficiency is observed, and secondary IgM deficiency accompanied by such autoimmune diseases as SLE,[5] Crohn's disease,[6] multiple myositis,[7] and Hashimoto's disease.[8]

Until now, IgM deficiency has been found to be complicated by deficiencies such as IgG2, IgA, or IgG 1, but never by IgG4. The clinical symptoms of IgG4 deficiency include repeated infections, as reported in other IgG subclass deficiencies.[9] As few studies have reported selective IgM deficiency from among the various other types of primary immunodeficiencies, the detailed mechanism of this disorder remains to be clarified. In this study, we report on a patient with selective IgM deficiency in whom various dermal findings, repeated bronchial pneumonia induced by a

[1]First Department of Medicine and [2]Department of Infection and Host Defense, Shinshu University School of Medicine, Nagano, Japan.
Correspondence: Kazunaga Agematsu, MD, Ph.D., Department of Infectious Immunology, Shinshu University School of Medicine, 3–1–1 Asahi, Matsumoto, Nagano 390–8621, Japan.
Email: agemts_k@sch.md.shinshu-u.ac.jp
Received 20 December 2006. Accepted for publication 3 August 2007.

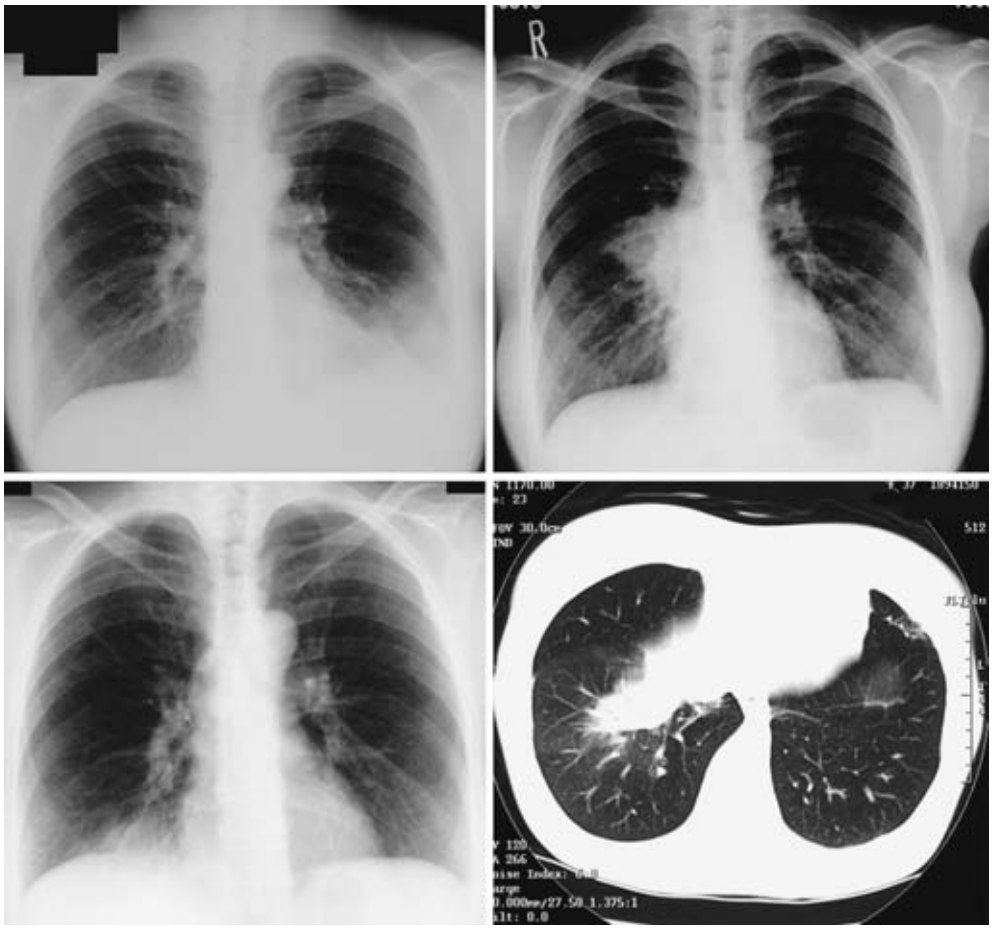

Fig. 1 A chest radiograph taken on April 18, 2002 shows an infiltrative shadow in the left lower lobe (upper left). A chest radiograph taken on June 22, 2003 shows an infiltrative shadow in the right middle lobe (upper right). A chest radiograph taken on admission (November 22, 2003) shows an infiltrative shadow in the left lower lobe (lower left). A chest CT taken on November 25, 2003 shows ground-glass attenuation around the infiltrative shadow in the right lower lobe (S^8) (lower right).

fibroepithelial bronchial polyp, and IgG4 deficiency were concurrently observed for several years, and compare this case with cases previously reported in the literature on IgM deficiencies.

CLINICAL SUMMARY

The patient was a 37-year-old woman. She had no bronchial asthma or food allergy. She had a history of allergic sinusitis and systemic pigmentation of the skin which started at the age of 20 years. With regard to her family history, her mother had gastric cancer and allergic rhinitis. She did not smoke habitually and consumed alcohol on occasion. In 1994 at the age of 28 years, the patient was admitted to a local clinic for pneumonia, and after that she frequently caught colds. In 1998, the patient was admitted for pneumonia twice, and admitted again in 2002 (Fig. 1 upper left). These repeated episodes occurred in different lung fields. However, in May and June 2003, pneumonia repeatedly developed in the right middle lung field (Fig. 1 upper right) and thoracic computed tomography (CT) revealed occlusive changes in the right B6 area. Therefore, in August 2003, the patient was referred to our department for further examinations. Bronchoscopy revealed a polyp in the right B6 orifice, which was suggested to be a fibroepithelial polyp following a biopsy (Fig. 2), and on August 14, a transbronchial polypectomy was performed.

Thereafter, follow-up was continued on an outpatient clinic basis. In November 2003, fever, cough, and sputum recurred, and the patient consulted our department. A chest X-ray showed infiltration in the right inferior lung field (Fig. 1 lower left), which was localized in the right S8 to S9 areas on thoracic CT (Fig. 1 lower right), demonstrating that the pneumonia had recurred in a segment different from the previous polyp site. Therefore, on November 21, 2003, the patient was admitted to our department for fur-

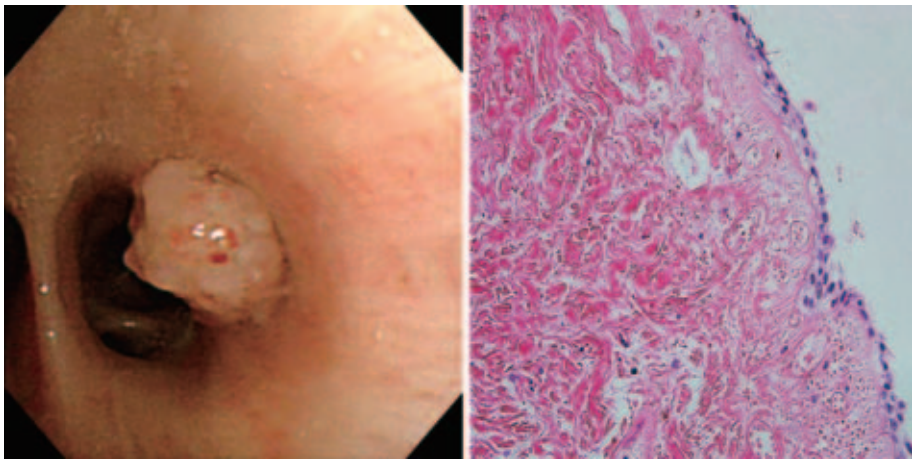

Fig. 2 Bronchoscopy findings show a polypoid mass with a smooth surface narrowing the right B^6 (left). Microscopic examination of the tumor showed characteristics of a fibroepithelial polyp (right).

ther examinations.

The pathological findings of the skin, including erythema, most strongly suggested drug-induced exanthema. Therefore, DLST with sodium valproate was performed along with oral administration of Claritin, but to no effect, indicating another mechanism may have been involved in pigmentation. To treat the dermal findings, the above drugs were discontinued in favor of oral administration of an antihistamine agent and application of a corticosteroid, which relieved the erythema and pruritus, although pigmentation persisted. Concerning the patient's bouts of pneumonia, although there were no recurrent bronchial polyps, the infection occurred in another segment, suggesting the relapse of a series of pneumonias. Treatment with SBT/ABPC at 6 g/day and CLDM at 1.2 g/day was started. In the sputum, *Staphylococcus epidermidis* was detected, but it was sensitive to SBT/ABPC and CLDM in a drug sensitivity test. Nine days after admission, the patient was negative for inflammatory response with improvement of symptoms. Lastly, in terms of the patient's antibody immunodeficiency disorder, prophylactic oral administration of clarithromycin at 400 mg/day was started, and the now discharged patient is doing well.

PATHOLOGICAL FINDINGS

On admission to our department, her height and body weight was 158 cm and 57 kg, respectively. She had a body temperature of 39.4℃, blood pressure of 110/60 mmHg and regular pulse of 126/min. There was no superficial lymph node swelling. Respiratory sounds were clear in both lungs. There were no other abnormalities or abnormal neurological findings. Dermal findings showed systemic pigmentation along with erythema in both forearms (not shown), the back (Fig. 3 left) and lower legs (Fig. 3 right). In the forearms, annular erythema was noted, and bleb formation was observed in the lower legs. A skin biopsy suggested necrosis of epidermic cells, liquefaction degeneration related to lymphocytic attacks at the border between the epidermis and the corium, and infiltration of lymphocytes and eosinophils around blood vessels involving the middle layer of the corium. Collectively, the findings suggested drug-induced exanthema (Fig. 4). The peripheral blood leukocyte count was 13,900/μl with 86.4% neutrophils and a C reactive protein level of 3.97 mg/dl (Table 1). IgM and IgG4 levels were 3.0 mg/dl and less than 2.0 mg/dl, respectively, suggesting IgM/IgG4 deficiency. IgG subclass was measured by ELISA using monoclonal antibodies. The patient was positive for IgE specific against *Staphylococcus aureus* enterotoxin A/B. Bronchoscopic findings showed no changes from the vocal cords to segmental bronchus. No recurrent polyp was detected in the right B6 orifice. A brush was inserted through the right B8 area, and bronchoalveolar lavage (BAL) was performed. Cytodiagnosis showed a large number of neutrophils and scattered eosinophils. Marked inflammation was noted, although there were no atypical cells (Class II). In the collected bronchoalveolar lavage fluid (BALF) (collection rate: 89/150 ml), the distribution of macrophages, lymphocytes, neutrophils, and eosinophils was 63.2%, 14.1%, 7.1%, and 14.6%, respectively. In the sputum culture, only *α-Staphylococcus* (±) and indigenous bacteria were detected. Bone marrow findings, in one particular clot, showed that the normocellular marrow number of megakaryocytes was very small and the number of eosinophils large. A smear showed that the incidence of blasts was 1.8%, and eosinophils were increased to 18%, although no atypical cells were seen. There were also no tumorous changes. With regard to neutrophil function, there were no abnormalities in neutrophil

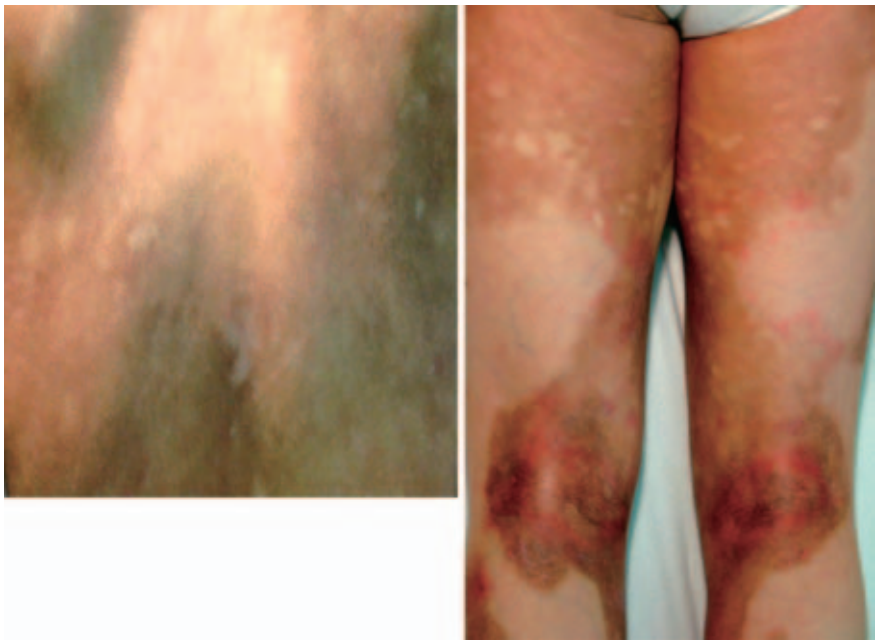

Fig. 3 Clinical aspects of a patient with plaque-like pigmentation, erythema, and blisters over the whole body. Back (left) and the back of the knees (right).

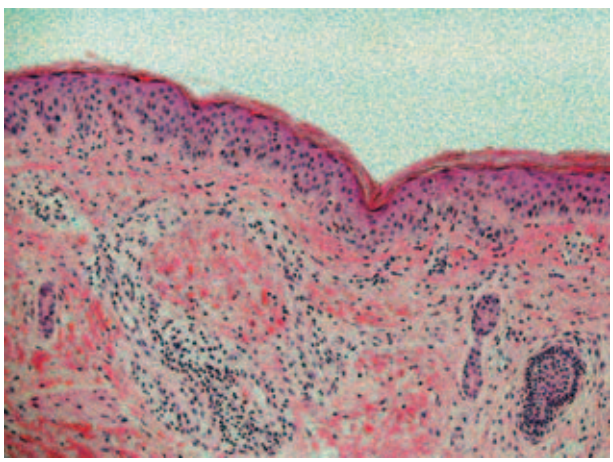

Fig. 4 Skin biopsy. Histologically, the lesions consisted of a perivascular and periadnexal lymphohistiocytic infiltrate with a few eosinophils.

chemotaxis either. Bactericidal activity was observed in 89.6% of the cells (>70%), and phagocytosis was observed in 44.7% (70–90%). On peripheral flow cytometric analysis (Table 2), the proportion of $CD20^+$ B cells in peripheral lymphocytes was 3.7%. There were no abnormalities in the number of T cells, NK cells, or monocytes. In B cell subpopulations, the proportions of class switched memory B cells (IgD^-CD27^+) and IgM (IgD^+CD27^-) memory B cells were markedly decreased to 8% and 6%, respectively. Blastogenic response to peripheral blood lymphocyte mitogens (Table 2) showed mildly excessive responses to T cell mitogens, phytohemagglutinin (PHA), and concanavalin A (Con A).

DISCUSSION

Due to its extremely low incidence, the criteria for selective IgM deficiency have not yet been firmly established, although a previous report proposed that patients with an IgM level of 20 mg/dl or less should be regarded as having selective IgM deficiency.[10] Functional disorders of B cells, hyperdynamia of regulatory T cells, and dysfunction of helper T cells may also be involved in the etiology; B cell functional disorders might reflect disorders in differentiation from IgM-positive B cells to IgM-producing cells.[11] In hyperergasia of regulatory T cells, IgM production by B cells is inhibited as IgM-specific regulatory function is enhanced in T cells from patients with IgM deficiency.[12] Lastly, in dysfunctions of helper T cells, IgM^+ mature B cells fail to differentiate into IgM-producing plasma cells in the presence of antigen stimuli and stimuli by helper T cells. It has been reported that helper T cell dysfunction reduces the level of IgM.[4] In our patient, general T cell functions were normal, although the number of memory B cells was decreased and naive B cells increased.

Several studies have previously reported and classified IgM deficiency. Our patient had no history of autoimmune disease, as demonstrated in secondary IgM deficiency, so primary IgM deficiency was suggested. Our literature search of English and Japanese databases (1974–2004) revealed that only 22 patients with primary selective IgM deficiency, including our

Table 1 Laboratory findings on admission

Hematology		Serology		IgE RAST	
WBC	13,900 /μl	CRP	3.97 mg/dl	Dermatophagoides-farnase	Class 3
Neutro	88.4 %	IgG	1,156 mg/dl	Cat	Class 2
Lympho	4.0 %	IgM	3.0 mg/dl	Yomogi	Class 2
Mono	2.8 %	IgA	291 mg/dl	S.aureus	
Eosino	4.7 %	IgE	3418 IU/ml	enterotoxin A	Class 2
Baso	0.1 %	IgD	7.6 mg/dl	S.aureus	
RBC	4.17×10^6 /μl	C3	101 mg/dl	enterotoxin B	Class 3
Hb	12.9 g/dl	C4	23.8 mg/dl	DLST	
Plt	12.7×10^4 /μl	CH50	50.6 U/ml	Sodium valproate	negative
ESR	6 mm/1 h	LE	(−)	Loratadine	negative
	14 mm/2 h	ANA	(−)	Blood gas analysis (room air)	
Biochemistry		Homogeneous pattern		PH	7.449
TP	6.4 g/dl	Myco IgM Ab	(−)	$PaCO_2$	36.2 torr
Alb	3.7 g/dl	Candida Ag	(−)	PaO_2	62.0 torr
α1-gl	2.8 %	Aspergillus Ab	(−)	HCO_3	24.7 torr
α2-gl	8.2 %	Cold test	< ×4	BE	1.4 torr
β-gl	10.2 %	HBs-Ag	(−)	SaO_2	92.5 %
γ-gl	16.4 %	HCV	< 0.5 KIU/ml	BALF	
BUN	9.0 mg/dl	TPHA	(−)	Mϕ	63.2 %
Cr	0.57 mg/dl	βD glucan	2.90 pg/ml	Neut	7.1 %
AST	21 IU/l	Endotoxin	1.44 pg/ml	Lymph	14.1 %
ALT	16 IU/l	IgG subclass		Eos	14.6 %
γ-GTP	13 IU/l	IgG1	942 mg/dl	CD4/CD8	1.81
LDH	287 IU/l		(538 − 1,244)	Total cell count	4.76×10^4 /ml
ALP	153 IU/l	IgG2	321 mg/dl	Recovery rate	59.3 %
CK	197 IU/l		(254 − 820)		
Na	138 mEq/l	IgG3	85 mg/dl		
K	3.4 mEq/l		(7 − 117)	Culture (sputum)	
Cl	105 mEq/l	IgG4	< 2.0 mg/dl	Staphylococcus-epidermidis	(1 +)
Glu	104 mg/dl		(5 − 105)		

Table 2 Lymphocyte surface markers of peripheral blood lymphocytes and lymphocyte proliferation

lymphocyte markers		lymphocyte proliferation	
CD2	88.5 % (71 − 91%)	Phytohemagglutinin (PHA)	58,157 cpm (26,000 − 53,000 cpm)
CD3	78.9 % (58 − 84%)	Control	157 cpm (70 − 700 cpm)
CD4	58.0 % (28 − 56%)		
CD8	30.0 % (17 − 44%)		
CD4/CD8	1.93 (0.6 − 2.9)	Concanavalin A (Con A)	49,689 cpm (20,000 − 48,000 cpm)
CD20	3.7 % (5 − 25%)	Control	157 cpm (70 − 700 cpm)
B cell subset			
$IgD^+ CD27^-$ B cells	8 3 %		
$IgD^+ CD27^+$ B cells	6.0 %		
$IgD^- CD27^+$ B cells	8.0 %		

patient, have been reported, and their characteristics are summarized in Table 3. Patient age at the time of diagnosis of primary IgM deficiency ranged from 7 to 85 years and the mean ± SD age was 35.86 ± 23.80 years. The mean ± SD serum IgM level was 13.35 ± 10.87 mg/dl, which is lower than the reported data (29.74 ± 8.68) by Goldstein MF *et al*.[3] This disorder was more frequently observed in men (male to female ratio 17 : 5). Of these, the titers of antibodies other than IgM were increased in 11 patients; levels of IgE, IgD, IgG and IgA were increased in 7, 4, 3, and 2 patients, respectively. The mean ± SD serum IgE level was 1203.25 ± 2200.21 μ/ml in the 7 patients with an increase in IgE levels, and dermal find-

Table 3 Profiles of patients with primary selective IgM deficiency

Case	Age	Sex	IgM	IgG	IgA	IgD	IgE	Associated disease	References
1	10	M	9	920	281	ND	195	Atopic hematuria	Iikura; 1974
2	85	M	17	1165	289	N.R	N.R	Hypertension	Endo M; 1981
3	7	M	5.8	1800	121	36	51	Otitis media (P. aeruginosa)	Hirao; 1981
4	13	M	6.3	790	200	63	550	Meningitis (α-streptococcus)	Hirao; 1981
5	14	M	6.9	370	192	42	6.2	Meningitis (α-streptococcus)	Hirao; 1981
6	13	M	8	1980	407	N.R	N.R	Mental retardation with epilepsy	Miura; 1986
7	16	F	< 4	2305	688	ND	8900	Atopic dermatitis, aphthous stomatitis, respiratory infection	Mayumi; 1986
8	42	M	10	3798	590	ND	1300	Pyelonephritis	Inoue; 1988
9	48	M	10	1641	243	2	154	Pneumonia	Inoue; 1988
10	58	M	20	972	93	5	208	Urinary infection, tuberculosis	Inoue; 1988
11	71	F	11	1726	412	2	130	Urinary infection, pneumonia	Inoue; 1988
12	73	F	14	1248	206	0	30	Urinary infection, bronchitis	Inoue; 1988
13	9	M	39	530	N.R	ND	940	Bronchitis, rhinitis, skin eosinophilic infiltration, hyper IgG4	Conrad H; 1991
14	50	M	18	1534	283	1	2000	Cholangitis, gout, liver abscess, dermatitis	Yamasaki; 1992
15	57	M	6	1413	288	0	59	Diabetes mellitus	Yamasaki; 1992
16	22	M	32	2127	245	2.5	394	Streptococcal infection	Yamasaki; 1992
17	34	M	1	1314	168	ND	ND	Psoriasis pustulosa, chronic tonsillitis, bronchitis	Yamasaki; 1992
18	57	M	0.4	1747	462	2.5	2000	Diabetes mellitus, polyarthritis	Yamasaki; 1992
19	37	F	34	1446	340	ND	ND	Asymptomatic	Yamasaki; 1992
20	26	M	6	1164	572	102	120	Paranasal sinusitis, pneumonia, pyelonephritis	Yoneda; 1997
21	10	M	23	900	86	ND	ND	G-6-P def., dehydrogenase, sinobronchitis	Hayyam; 2001
22	37	F	3	1156	291	7.6	3418	IgG4 deficiency, atopic dermatitis, paranasal sinusitis, bronchial polyp	Our case

Age: years, Sex: M; male. F; female, ND: not done, N.R: normal ranges; IgM: 60－280 mg/dl, IgG: 800－1800 mg/dl, IgA: 90－450 mg/dl, IgD: 0－15 mg/dl, IgE: < 400 IU/ml

ings were observed in 3 patients. An infection developed in 17 of the 22 patients; upper airway/respiratory infections were observed in 11 patients (50.0%), and infections of the urinary system were seen in 5 patients (22.7%). According to Yamasaki *et al*.[13] and Schopfer *et al*.,[14] patients with selective IgM deficiency frequently showed an increase in IgE levels and developed repeated atopic dermatitis and *Staphylococcus aureus*-associated pyoderma, all of which were seen in our patient. Disorders in antibody production may lead to repeated chronic infection, inducing an excessive response to bacterial infection and thus increasing the level of IgE since the response of B cells to *Staphylococcus aureus* Cowan strain I (SAC) is markedly reduced in patients with IgM deficiency. The involvement of disorders in RNA processing in the disease etiology has also been suggested.[4]

In our patient, several dermal changes were observed, such as atopic pigmentation, erythema, and blebs. As the patient had specific IgE against *Staphylococcus aureus* enterotoxin A/B and high levels of serum IgE, hyper IgE syndrome was ruled out. Given that the patient's dermal symptoms developed during adulthood, her pathological changes differed slightly from atopic dermatitis, suggesting drug exanthema-like changes. However, a definitive diagnosis is yet to be made.

Interestingly, of the 22 patients with IgM deficiency surveyed in our study (Table 3), not a single patient concurrently developed IgG4 deficiency like our patient. Repeated respiratory infection as in our case, asthma and food allergy are consistent with typical clinical symptoms of IgG4 deficiency.[9] Since defects in the immunoglobulin heavy chain constant region (IGHC)[15] and partial defects or mutations in the IgGHC4 gene[16] have also been reported in IgG4 deficiency, analysis of the IgGHC4 gene should be investigated in the present patient in the future.

Lastly, the concurrent development of IgM deficiency and a bronchial polyp could not be confirmed in any publication, as seen in Table 3. The histology in our patient suggested a fibroepithelial polyp, which is a polyp-like benign tumor associated with outgrowth of the interstitial collagen fibers, and is frequently detected in the dermatological, gynecological, and urological fields.[17] It has been reported that fibroepithelial polyps readily occur in repeated inflammation/friction sites, and most patients show a good course after resection. To date, there has been no relapse in our patient. Although the association between a solitary polyp and IgM deficiency is unclear, repeated IgM deficiency-related airway infections

should be considered an etiological factor for the inflammatory polyp.

REFERENCES

1. Hobbs JR, Hons B Sc. IgM deficiency. In: Bergsma D, Robert E (eds). *Immunodeficiency in man and animals.* New York: Krieger Publishing, 1977;112-114.
2. Iwata T. [Nationwide registry of primary immunodeficiency diseases.] Summary of research team, in Japanese Ministry of Health, about special diseases and primary immunodeficiency syndrome. 2000;5-8 (in Japanese).
3. Goldstein MF, Goldstein AL, Dunsky EH *et al*. Selective IgM immunodeficiency: retrospective analysis of 36 adult patients with review of the literature. *Ann. Allergy Asthma Immunol.* 2006;**97**:717-730.
4. Ozawa T, Kondo N, Motoyashi F *et al*. Preferential damage to IgM production by ultraviolet B in the cells of patients with Bloom's syndrome. *Scand. J. Immunol.* 1993; **38**:225-232.
5. Takeuchi T, Nakagawa T, Maeda Y *et al*. Functional defect of B lymphocytes in a patient with selective IgM deficiency associated with Systemic Lupus Erythematosus. *Autoimmunity* 2001;**34**:115-122.
6. Morita M, Saibara T, Nakazawa Y *et al*. A case of Crohn's disease associated with selective IgM deficiency. *Nihon Shoukakigakkaisi* 1984;**81**:1070-1075 (in Japanese).
7. Sugimoto K, Dohi K, Ohubo H. A case of polymyositis with acquired selective IgM deficiency, Mycobacterium marinum infection and severe interstitial pneumonitis. *Saishin Igaku* 1983;**38**:2306-2312 (in Japanese).
8. Shigeru K, Mari T, Yasumitsu N *et al*. Selective IgM deficiency in a Patient with Hashimoto's Disease. *Intern. Med.* 1993;**32**:302-307.
9. Heiner DC. IgG4 Immunodeficiency. *New England and regional allergy proceedings* 1988;**9**:43-50.
10. Hokibara S, Komiyama A. Selective IgM deficiency. *Ryoikibetsu Shokogun Shirizu* 2000;**32**:92-93.
11. Inoue T, Ishibashi H, Kudo J *et al*. Functional and phenotypical analysis of the lymphocytes in 10 patients with selective IgM deficiency. *Nihon Menekigakkaisi* 1988;**11**: 236-243 (in Japanese).
12. Moffitt JE, Guill MF, Wray BB *et al*. Effect of interleukin-2 and mitogen on *in vitro* immunoglobulin production by peripheral blood lymphocytes from patients with selective IgM deficiency. *Ann. Allergy* 1988;**61**:424-427.
13. Yamasaki T. Selective IgM Deficiency: Functional Assessment of Peripheral Blood Lymphocytes *in Vitro*. *Intern. Med.* 1992;**31**:866-870.
14. Schopfer K, Baerlocher K, Price P *et al*. Staphylococcal IgE antibodies, hyperimmunoglobulinemia E and Staphylococcus aureus infection. *N. Engl. J. Med.* 1979;**12**:835-838.
15. Gallina R, Bottaro A, Boccazzi C *et al*. The genetics of IgG4 deficiency: role of the immunoglobulin heavy chain constant region and HLA loci. *Eur. J. Immunol* 1992;**22**: 227-233.
16. Takamoto M, Agematu K. [IgG subclass deficiency.] *Ryoikibetsu Shokogun Shirizu* 2000;**32**:89-91 (in Japanese).
17. Otuka K, Imamura H, Miyakawa S. A Hard Tumor on the Chest. *Jpn. J. Dermatopathol.* 2000;**16**:34-37.