

Rapid communications

Hypogammaglobulinemia and anemia 18 years after thymoma resection

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Immunodeficiency with a thymoma (Good's syndrome) is a rare condition occurring in 7% to 13% of patients with adult-onset hypogammaglobulinemia. In 80% of cases, hypogammaglobulinemia is detected within 5 years of the identification of the thymoma. A 70-year-old man was found to have hypogammaglobulinemia 18 years after a thymoma had been resected. Cellular immunophenotyping revealed there were no detectable B cells, decreased CD4⁺ cells, and increased CD8⁺ cells. Both CD4⁺ and CD8⁺ subsets expressed increased populations of CD38⁺ DR⁺ cells and CD45RO⁺ cells. The CD8⁺ CD28⁺ population was markedly reduced. Inducible cytokine production by the patient's peripheral blood mononuclear cells revealed decreased IL-2, IL-10, and interferon- γ production. These data suggest that patients with Good's syndrome have activated memory T cells that have dysregulated cytokine production. (*J Allergy Clin Immunol* 1997;100:846-8.)

Key words: Hypogammaglobulinemia, Good's syndrome, thymoma, immunodeficiency

Good's syndrome was first described in 1954 by Robert Good, MD,¹ who reported an association of immunodeficiency with thymoma. Good's syndrome occurs in 7% to 13% of patients with adult-onset hypogammaglobulinemia and is usually diagnosed between the ages of 40 and 70 years.² Recurrent sinopulmonary infections are common. Twenty-five to thirty-five percent of these patients will have diarrhea.³ In 80% of the cases hypogammaglobulinemia is identified either concomitantly with the thymoma or within 5 years of detection of the thymoma. The development of thymoma in Good's syndrome is unrelated to the hypogammaglobulinemia because patients with X-linked hypogammaglobulinemia are not at increased risk of having thymomas. Previous studies have reported that peripheral blood B cells are frequently undetectable,^{4,5} and T-cell subsets are quantitatively altered in patients with Good's syndrome.^{2,3} We were interested in extending these observations in a

Abbreviations used

IFN:	Interferon
PBMC:	Peripheral blood mononuclear cell
PHA:	Phytohemagglutinin

patient with Good's syndrome by examining not only markers of T-cell maturation and activation, but also in vitro cytokine production by the patient's peripheral blood mononuclear cells (PBMCs).

CASE REPORT

In 1976, a 58-year-old man without symptoms was found to have a mediastinal mass. At resection the mass was diagnosed as a teratoma. He was relatively well until September 1994 when he presented with symptoms of lethargy, diarrhea, and cough. Sequential chest radiographs revealed progressive infiltrates, bilateral pleural effusions, and mediastinal lymphadenopathy. Cultures obtained at bronchoscopy were negative. A diagnosis of bronchiolitis obliterans with organizing pneumonia was made. Quantitative immunoglobulin analysis revealed hypogammaglobulinemia, and IgG antibody titers to tetanus, diphtheria, *Haemophilus influenzae* B, and a panel of pneumococcal serotypes were undetectable. No peripheral blood B cells (CD19⁺) were detectable.

After the patient was found to have hypogammaglobulinemia, infusions of intravenous immunoglobulin were initiated, which resulted in clinical improvement. A subsequent computed tomographic scan of the chest revealed the presence of a mass, and a diagnosis of Good's syndrome was suspected. Within 3 1/2 months of starting intravenous immunoglobulin, profound anemia and thrombocytopenia developed. Because of frequent transfusion requirements the mass was resected. The pathologic evaluation confirmed the mass to be a thymoma. These findings prompted a review of the slides from the thymic mass that had been resected 18 years earlier. This revealed the tissue to be a thymoma and not a teratoma.

METHODS

PBMCs were isolated from heparinized blood by Ficoll-Hypaque (Organon Teknica, Durham, N.C.) density centrifugation and washed twice in phosphate-buffered saline. Viability was then determined by trypan blue dye exclusion. PBMCs were

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suspended in RPMI (Gibco, Grand Island, N.Y.) containing 5% gentamicin sulfate, 1% glutamine, and 10% fetal bovine serum.

Lymphocyte phenotyping was performed by staining PBMCs with horse peroxidase-conjugated monoclonal antibodies (CD3, CD4, CD8, CD25, CD28, CD38, HLA-DR, CD45RO), and CD45RA). Lymphocyte populations were analyzed by using three-color flow cytometry. Normal control values were established by performing identical analysis with six healthy control subjects.

In vitro cytokine synthesis studies were performed with PBMCs (1×10^6 cells/well) cultured in 24-well tissue-culture plates (Costar, Cambridge, Mass.) in 1 ml of medium followed by stimulus for 48 hours in a humidified atmosphere of 5% CO₂ at 37° C. Stimuli included phytohemagglutinin (PHA) (Sigma, St. Louis, Mo.) at 25 µg/ml and anti-CD3 OKT3 (Ortho Diagnostics, Raritan, N.J.) at 0.4 µg/ml. Cultures for IL-2 contained anti-IL-2 receptor (anti-Tac) monoclonal antibodies (purified from the ATCCHB8335 clone by using the Immuno-pure kit, Pierce, Rockford, Ill.) at a final concentration of 10 µg/ml to block IL-2 consumption. Decanted culture supernatants were further clarified by centrifugation and stored at -70° C until assayed.

Supernatants were assayed by using commercially available enzyme immunoassay kits for IL-2 (R & D Systems, Minneapolis, Minn.), IL-4 (Medgenix, Fleurus, Belgium), and interferon (IFN)-γ (Medgenix). IL-10 levels were analyzed with an enzyme immunoassay devised in the laboratory by using anti-IL-10 capture and detection monoclonal antibodies (PharMingen, San Diego, Calif.).

RESULTS

Lymphocyte immunophenotyping with three-color flow cytometry demonstrated an expansion of the CD8 subset resulting in a CD4/CD8 ratio of 0.3 (Table I). The CD8⁺ lymphocyte population expressing HLA-DR was increased as were CD4⁺ and CD8⁺ subsets coexpressing CD38 and HLA-DR. The CD8⁺/CD28⁺ subset was decreased compared with controls, whereas both CD4⁺ and CD8⁺ subsets expressing CD45RO were increased. A reciprocal decrease in CD4⁺ and CD8⁺ subsets coexpressing CD45RA was also detected.

Cytokine studies with PBMCs stimulated in vitro with either PHA or anti-CD3 (OKT3) revealed altered cytokine production. Both anti-CD3 and PHA-stimulated PBMCs secreted less IL-2, IL-10, and IFN-γ than controls (Table I).

DISCUSSION

The patient described in this report had hypogammaglobulinemia and profound hematologic abnormalities 18 years after an asymptomatic mediastinal mass was reported to be a teratoma. As the course of the disease progressed, a mediastinal mass was again demonstrated on computed tomography of the chest, and a subsequent biopsy revealed that the mass was a thymoma. Review of the slides from 18 years earlier revealed that the teratoma was in fact a thymoma. Thymomas are neoplasms of the thymic epithelium that generally arise in the anterior mediastinum. Thymomas in Good's syndrome are predominantly of the spindle cell type with only 10% being malignant.

TABLE I. Good's syndrome

	Quantitative immunoglobulin analysis	Patient	Control subjects
IgG (mg/dl)	115 (610-1622)		
IgA (mg/dl)	<8 (71-350)		
IgM (mg/dl)	9 (35-213)		
Immunophenotyping (absolute lymphocyte count 2627 per mm ³ [1140-4430])			
CD19 ⁺ (%)		0	(3-23)
CD3 ⁺ 4 ⁺ (%)		30	46 (6)*
CD3 ⁺ 8 ⁺ (%)		58	26 (6)
CD8 ⁺ 38 ⁺ DR ⁺ (%)		58	6 (2)
CD4 ⁺ 38 ⁺ DR ⁺ (%)		18	3 (2)
CD8 ⁺ 28 ⁺ DR ⁻ (%)		16	77 (14)
CD8 ⁺ 45RO ⁺ RA ⁻ (%)		58	13 (11)
CD4 ⁺ 45RO ⁺ RA ⁻ (%)		63	28 (4)
CD8 ⁺ 45RA ⁺ RO ⁻ (%)		18	49 (19)
CD4 ⁺ 45RA ⁺ RO ⁻ (%)		6	35 (11)
Cytokines			
IL-2 (pg/ml)			
Medium		3	10 (9)
PHA		156	968 (361)
OKT3		115	215 (145)
IL-4 (pg/ml)			
Medium		1	3 (9)
PHA		62	36 (23)
OKT3		1	3 (9)
IL-10 (pg/ml)			
Medium		5	85 (156)
PHA		300	5571 (4104)
OKT3		126	1436 (1407)
IFN-γ (IU/ml)			
Medium		4	2 (3)
PHA		39	62 (64)
OKT3		20	131 (86)

*Mean of six normal control subjects (1SD).

As had been previously reported in other patients with Good's syndrome,^{4,5} lymphocyte phenotyping studies revealed no detectable peripheral blood B lymphocytes in our patient. Similar to patients in other reports, this patient had an inverted CD4/CD8 ratio and an expansion of the CD8⁺ DR⁺ lymphocyte subset.^{2,3} The altered CD4/CD8 ratio was caused by an expanded CD8⁺ population and reduced numbers of CD4⁺ cells.

The cellular studies in this report demonstrate an expansion of both CD4⁺ and CD8⁺ subsets coexpressing the activation markers CD38 and HLA-DR. Furthermore, expansion of CD4⁺ CD45RO⁺ and CD8⁺ CD45RO⁺ subsets with a reciprocal decline in the CD45RA⁺ T-cell population suggests that memory T cells predominate. Last, the CD8⁺ subset coexpressing the costimulatory activation molecule CD28 was decreased in this patient.

An anergy profile using six intradermal antigens (tet-

anus, 5 TU purified protein derivative, mumps, histoplasmin, *Candida*, and trichophyton) at a time when the patient was clinically well revealed that he was anergic. In addition to cutaneous anergy, in vitro studies of PHA-stimulated cytokine production by the patient's PBMCs demonstrated profound defects of both IL-2 and IL-10 production. The production of IFN- γ after PBMC stimulation with anti-CD3 was also decreased. These data suggest that patients with Good's syndrome may have depressed T-cell function as evidenced by cutaneous anergy and diminished inducible cytokine production.

Because of the clinical course that suggested Good's syndrome and the subsequent demonstration of a thymoma, we were interested in reevaluating a teratoma removed from the anterior mediastinum of this patient 18 years previously. Once it had been identified as a thymoma, we were intrigued by the 18-year interval between the initial detection of the mass and the subsequent hypogammaglobulinemia and the profound cytopenias. Other reports have described intervals as long as 12 and 26 years between the identification of an asymptomatic anterior mediastinal mass and the subsequent detection of immunologic and hematologic abnormalities.^{8,9} Although most patients will have the detection of hematologic or immunologic abnormalities within 5 years of the identification of a thymoma, these observations suggest that physicians need to be sensitive to any clinical changes that might signal the progression of thymoma-related disease for intervals as long as 2 decades.

CONCLUSION

We describe a case of Good's syndrome with an interval of nearly 2 decades between the detection of the thymoma and profound immune dysregulation. As in previous studies, the patient had marked hypogammaglobulinemia, cutaneous anergy, and a reversed

CD4/CD8 ratio, with an expansion of the CD8⁺ DR⁺ subset. We found that our patient had expansion of a memory T-cell subset involving both CD4 and CD8 populations. The CD8 subset expressing the costimulatory molecule CD28 was decreased. Cytokine analysis found defective synthesis of IL-2, IL-10, and IFN- γ by the patient's mononuclear cells, which suggests that dysregulated cytokine production occurs in Good's syndrome.

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Brief communications

Latex allergy as a cause of eosinophilia in cerebrospinal fluid in a child with a ventricular shunt

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CASE REPORT

A 6-year-old boy (G.B.) had been born prematurely after 36 weeks of gestation with a birth weight of 2010 gm. Because of intraventricular hemorrhage he had undergone surgery and received a ventricular-atrial shunt at the age of 4 weeks. During the following years, a total of 15 operations were necessary for treatment of infections or malfunctioning of the shunt systems. From infancy on, he had bronchial asthma and atopic dermatitis. On contact with plasters, urticarial wheals (extending beyond the area of contact) could be observed.

At the age of 6 years, a massive eosinophilia of 80% in cerebrospinal fluid (CSF) was detected (Fig. 1). Peripheral blood eosinophil count was 25%. Total IgE in serum (measured by Pharmacia CAP System) was elevated (961 kU/L). Specific IgE to inhalant allergens was detectable. In view of his atopic disposition and the underlying disease, we determined specific IgE to latex, which was found to be very high (95.1 kU/L). This suggested that a latex allergy might be responsible for the eosinophilia in CSF. Subsequent measurements of total and

Abbreviation used

CSF: Cerebrospinal fluid

specific IgEs in CSF did indeed show that specific IgE to latex was nearly as high as that in serum (73.0 kU/L). Shunt revision after identification of latex allergy was performed with latex-free products.

The few studies in the literature on the relationship between specific IgE in serum and CSF revealed little about the location of IgE synthesis and the clinical relevance of IgE in CSF.^{1,2,3} We therefore investigated IgE in six other children with ventricular shunts (Table I).

DISCUSSION

In our view the following aspects point to latex allergy as a cause of the eosinophilia seen in our patient: (1) the patient showed clear signs of a symptomatic latex allergy with urticarial wheals after contact with plasters; (2) although total IgE was detectable in CSF (but less than 10% of serum value), the specific IgE in CSF was nearly as high as that in serum; (3) specific IgE to latex represents 84% of total IgE in CSF; and (4) none of the other patients showed specific IgE in CSF, despite relevant levels in serum (Table I). In addition, no other

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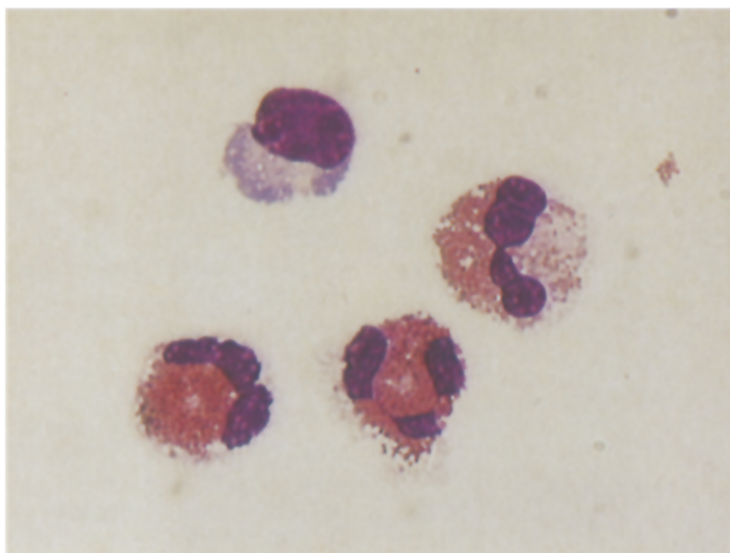


FIG. 1. CSF showing predominance of eosinophils.

TABLE I. IgE levels in serum and CSF

Subject	Total IgE serum	Total IgE CSF	Latex IgE serum	Latex IgE CSF	SX 1 Serum	SX1 CSF	fx 5 Serum	fx 5 CSF
E.T.	2.7	<2.0	<0.35	<0.35	<0.35	<0.35	<0.35	<0.35
F.S.	203.0	2.9	<0.35	<0.35	Pos.	<0.35	<0.35	<0.35
S.A.	34.6	<2.0	<0.35	<0.35	<0.35	<0.35	<0.35	<0.35
M.P.	119.0	<2.0	<0.35	<0.35	Pos.	<0.35	<0.35	<0.35
W.J.	169.0	<2.0	0.76	<0.35	Pos.	<0.35	<0.35	<0.35
H.M.	84.9	<2.0	12.5	<0.35	Pos.	<0.35	Pos.	<0.35
G.B.	961.0	87.4	95.1	73.0	Pos.	<0.35	Pos.	<0.35

All data are given in kilounits per liter: <0.35 kU/L = below detection limit for specific IgE; <2.0 kU/L = below detection limit for total IgE. SX 1, IgE screening test for eight inhalant allergens; fx 5, IgE screening test for six nutritional allergens; Pos., positive.

patient showed a CSF eosinophilia—including the two patients sensitized to latex in serum.

Our results indicate that IgE detected in CSF is not the consequence of a leaky hemato-encephalic barrier but has been synthesized locally. IgE may be produced by plasma cells in CSF deriving from lymphocytes, which we were able to detect in the differential cytologic specimens.

The source of latex leading to sensitization was probably not the shunt system because since 1989 these have been latex-free. We therefore suspect that repeated contact with glove powder containing latex during multiple operations established a long-term allergen depot as the probable cause.

In conclusion, this is the first report pointing to a local specific IgE production in CSF leading to a local men-

ingeal allergic reaction in the form of an eosinophilia. It should be considered that eosinophilia in CSF may be linked to latex allergy.

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Apnea as a manifestation of mast cell activation in an infant with mastocytosis

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Apnea in infancy is often associated with serious illnesses such as sepsis, neurologic disorders, or metabolic disturbances. Apnea may also occur in premature infants in the absence of identifiable disease. We describe a 5-month-old infant with recurrent episodes of

apnea preceding the onset of cutaneous lesions of mastocytosis. Elevation of the serum β -tryptase level after an episode of apnea suggests that mast cell activation may have been involved in the development of apnea in this patient.

CASE REPORT

The patient is a black male infant born at 36 weeks of gestational age. He experienced recurrent episodes of apnea commencing at 3 days of age, for which he was repeatedly evaluated in the local emergency department without a clear diagnosis and without any treatment instituted. At 5 months of age he had a generalized skin rash and demonstrated increased irritability. Three weeks later, he was admitted to a local

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