Good's Syndrome and Pernicious Anemia

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Abstract

In a rare case of Good's syndrome with pernicious anemia, one year after thymectomy, recurrent respiratory infections developed. Both panhypoglobulinemia and pernicious anemia were disclosed. An immunological analysis revealed the absence of circulating B cells, but T cell numbers and mitogenic responses were normal. Regular gammaglobulin and vitamin B₁₂ injections were successful in keeping the patient symptom free.

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Key words: thymoma, hypogammaglobulinemia, immunodeficiency

Introduction

Many diseases are associated with thymoma. The thymoma association with hypogammaglobulinemia occurs in 5% of thymoma patients and is described as Good's syndrome (1). Pernicious anemia occurs in 2–10% of hypogammaglobulinemia patients (2, 3). Thymoma with pernicious anemia is unusual and perhaps coincidental (1). The triad of thymoma, hypogammaglobulinemia, and pernicious anemia is a rare association, with only three cases reported previously (4–6). Here, a case of this triad as well as its features are presented.

Case Report

A 71-year-old man was admitted to our hospital in October 2000 with pneumonia associated with sepsis caused by *Klebsiella pneumoniae*. He had previously suffered from pneumonia in July 2000 and underwent thymectomy for a mediastinal thymoma in June 1999. Pathologic examination revealed an epithelial spindle cell type thymoma. A preoperative blood test showed hemoglobin at 11.8 g/dl and serum γ -globulin at 0.3 g/dl. Laboratory studies on admission revealed a leukocyte count of 2,700/mm³ (69% segmented neutrophils, 12% stab forms, 16% lymphocytes, and 3% monocytes), hemoglobin 11.5 g/dl, hematocrit 34.5%, mean corpuscular volume 111.2 μ m³, platelet

count 167,000/mm³, and C-reactive protein (CRP) 22.31 mg/dl. Serum protein electrophoresis showed the following values (in g/dl): total protein 5.2, albumin 3.5, α_1 -globulin 0.3, α_2 -globulin 0.6, β -globulin 0.4, and γ -globulin 0.1. Quantitative immunoglobulins (in mg/dl) were IgG 31 (normal range: 1,155 to 1,723), IgA <10 (normal range: 167 to 332), and IgM <10 (normal range: 82 to 160). Lymphocyte surface marker analysis in the peripheral blood showed a B-cell defect (CD19), normal T-cell numbers (CD3), and a normal CD4/CD8 ratio. The phytohemagglutinin (PHA)-induced lymphocyte responses were higher than in controls. The concanavalin A-induced lymphocyte responses were within the normal range. The serum vitamin B₁₂ level was 150 pg/ml (normal range: 233 to 914) and the serum folate level was 4.5 ng/ml (normal range: 2.4 to 9.8). The bone marrow was normocellular with megaloblast proliferation. The serum was negative for intrinsic factor antibodies and borderline for gastric parietal cell antibodies. Endoscopic examination showed atrophic pan-gastritis with no antral sparing. The gastric biopsy specimens showed loss of parietal and chief cells and replacement by cells resembling those of the intestinal mucosa (intestinal metaplasia) associated with submucosa lymphocyte infiltration. Based on the above findings, this case was diagnosed as thymoma with hypogammaglobulinemia (Good's syndrome) and pernicious anemia. The pneumonia was cured by intravenous meropenem injections for two weeks. The patient was treated with intramuscular vitamin B₁₂ and had a normal hemoglobin value within one month. Loading intravenous gammaglobulin infusion was given at 5 g/day (100 mg/kg/day) for two days, which raised the IgG level to more than 200 mg/dl. Currently, he is receiving intravenous gammaglobulin monthly at 5 g/month (100 mg/kg/month) in order to obtain a trough IgG of 200 mg/dl, and regular intramuscular vitamin B₁₂ (Table 1). He remains healthy one year after therapy initiation.

Discussion

At least 40% of thymoma patients have parathymic syndrome (1). Hypogammaglobulinemia has been reported in 5% of thymoma patients (1) and is commonly referred to as Good's syndrome. The coincidence of thymoma and pernicious anemia is uncommon and no causal relationship between the two is

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Table 1. Laboratory Data

Month/year	6/1999	10/2000	11/2000	12/2000	1/2001
WBC (/μl)	6,600	2,700	7,200	8,900	7,700
Hemoglobin (g/dl)	11.8	11.5	11.7	14.2	15.1
Mean RBC volume (fl)	108	111.2	112.4	105.8	99.3
CRP (mg/dl)		22.31	0.24	<0.2	0.29
Total protein (g/dl)	5.7	5.2	5.3		
γ-globulin (g/dl)	0.32	0.13	0.21		
IgG (mg/dl)		31	140	300	250
IgA (mg/dl)		<10	<10	<10	<10
IgM (mg/dl)		<10	<10	<10	<10
Vitamin B ₁₂ (pg/ml)		150	1,700		

known. The present case has the triad of thymoma, hypogammaglobulinemia, and pernicious anemia. Three triad case reports were found in the literature (4–6). The thymoma histological type was described in two reports, one lymphocytic-epithelial type (5) and one spindle-cell type (4) each. In a review by Jeunet and Good, 15 out of the 19 thymomas with hypogammaglobulinemia were spindle cell (7). The parathymic syndromes are predominantly associated with the spindle cell type (1). Serum levels of individual immunoglobulins were quantified in the three triad cases (4–6); two cases had normal IgM and low IgG and IgA levels, while one case had normal IgG and low IgA and IgM levels. In the present case, the IgG level was extremely low and both IgA and IgM were undetectable. Hypogammaglobulinemia in Good's syndrome does not improve after thymectomy (7).

Pernicious anemia (PA) is caused by vitamin B₁₂ deficiency due to autoimmune gastritis, and has been reported to coincide with 2–10% of patients with hypogammaglobulinemia (2, 3). There are some differences in clinical features between classical PA and PA associated with hypogammaglobulinemia (8). First, autoantibodies commonly present in classical PA are rarely found in PA patients with hypogammaglobulinemia. In a review by Wright and Sears (8), gastric parietal cell serum antibodies were found in only 2 out of 24 patients tested, and only 1 out of 20 patients had detectable intrinsic factor antibodies. Secondly, the atrophic gastritis of classical PA affects the stomach fundus, but spares the antrum (type A). In contrast, the gastric antrum is involved in the atrophic process (type B) in PA patients with hypogammaglobulinemia, suggesting that the gastric lesion pathogenesis may be different in these patients. Lastly, the diagnosis is made by age 30 in half of the PA patients with hypogammaglobulinemia, but in the 60s in most classical PA cases. The present patient is similar to those with PA with hypogammaglobulinemia previously reported with evidence of antral involvement with atrophic gastritis and the absence of autoantibodies, but he is much older than those with PA with hypogammaglobulinemia. This difference in onset age between the present patient and PA patients with hypogammaglobulinemia may be connected with the mean age (62 years) of Good's syndrome patients.

Autoimmune gastritis murine models have been established (9, 10). This gastritis develops in susceptible mouse strains after neonatal thymectomy. It also develops in neonatal mice treated with cyclosporine and in adult mice after thymectomy combined with irradiation, cyclophosphamide treatment, or immunization with murine gastric H⁺/K⁺-ATPase. CD4 T cells appear to be important in gastritis pathogenesis because transfer of these cells into naive mice results in gastritis and gastric H⁺/K⁺-ATPase serum autoantibodies. This gastritis occurs only when pathogenic T cells are transferred to immunocompromised mice. This observation, together with the induction of gastritis by thymectomy, immunosuppressive drugs, and irradiation, suggests that pathogenic T cells expand only in a lymphopenic host. Three out of 4 patients with Good's syndrome with PA developed PA 1 to 15 years after thymectomy (5, 6). Whether thymectomy induces PA under an immunodeficiency state of Good's syndrome is unknown.

Immunologically, patients with Good's syndrome have low or absent peripheral B cells and are often associated with cellular immune defects (11). They appear to develop opportunistic infections such as cytomegalovirus disease more frequently than patients with common variable immunodeficiency and other predominantly humoral immunodeficiencies (11). This may indicate an overall greater degree of immunodeficiency and may account for the higher mortality in Good's syndrome. The present patient has normal cellular immunity and is healthy while receiving intravenous immunoglobulin (IVIG). The optimal trough IgG level in immunoglobulin replacement therapy has been reported at 200 mg/dl (12) to 500 mg/dl (13). This patient received IVIG to obtain a trough IgG level of 200 mg/dl, which controlled all infections, except for mild chronic sinusitis. Interestingly, Wright and Sears (8) reported two patients with hypogammaglobulinemia and PA, in which decreased levels of serum immunoglobulins were reversed by vitamin B₁₂ injection. In the present case, the effect of vitamin B₁₂ therapy on gammaglobulins is unknown because intravenous gammaglobulins were given simultaneously.

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