Durable Hypogammaglobulinemia Associated with Thymoma (Good Syndrome)

Atsushi Kitamura¹, Yuichi Takiguchi¹, Naobumi Tochigi², Shun-ichi Watanabe¹, Seiichirou Sakao³, Katsushi Kurosu¹, Nobuhiro Tanabe¹ and Koichiro Tatsumi¹

Abstract

Good syndrome, characterized by hypogammaglobulinemia and acquired immunodeficiency, is a rare condition associated with thymoma. A 67-year-old woman, who 4 months previously had a thymoma resected, presented with generalized hypogammaglobulinemia with a severely decreased B cell population as demonstrated by flow cytometry. She was diagnosed as having bacterial mediastinitis associated with Good syndrome. For the subsequent 6 years, she suffered from repeated serious bacterial infections. As this paraneoplastic syndrome is not resolved by tumor removal, careful management with intensive infection-control using antibiotics and intravenous immunoglobulins is required for the long term. Serum immunoglobulin levels should be evaluated for patients with thymoma and suspected vulnerability to infection.

Key words: thymoma, Good syndrome, hypogammaglobulinemia, immunodeficiency, paraneoplastic syndrome

(Inter Med 48: 1749-1752, 2009)
(DOI: 10.2169/internalmedicine.48.2375)

Introduction

Patients with thymoma sometimes suffer from specific types of paraneoplastic syndrome or remote effects of cancer. They include myasthenia gravis, pure red cell aplasia, and hypogammaglobulinemia (Good syndrome) (1), with approximate occurrence of 30%, from 1.6 to 5%, and from 3 to 6%, respectively (2-5). The primary mechanism underlying these conditions is autoimmunity to acetylcholine in myasthenia gravis (2), and to erythrocytes in pure red cell aplasia (6). In Good syndrome, autoimmunity to B lymphocyte lineage causes severe deficiency in B lymphocytes and hypogammaglobulinemia, resulting in acquired immunodeficiency vulnerable especially to bacterial infection (7). In addition, some patients with Good syndrome display cellular immunodeficiency related to decreased T cells or presumed T cell dysfunction, resulting in vulnerability to fungal and viral infections (5). Although some paraneoplastic syndromes, in general, have been reported to recover by means of tumor removal, previous case reports have tended to indicate that hypogammaglobulinemia with Good syndrome, without improvement, extends even with tumor resection, up to as long as 9 years (5). The present case also has demonstrated repeated infections with prolonged hypogammaglobulinemia for as long as 6 years after complete resection of thymoma, providing additional evidence of this condition.

Case Report

A 67-year-old woman was admitted to our hospital because of persistent cough and fever. She had been healthy until 3 years earlier when she started to experience occasional repeated symptoms suggestive of respiratory infection. A chest X-ray taken 4 months earlier demonstrated a bulge at the left hilum, and a subsequent CT scan revealed an anterior mediastinal mass (Fig. 1). She was diagnosed with a thymoma, which was completely resected at a previous hospital. Pathological diagnosis of the resected tumor was non-invasive thymoma of type AB of WHO classification (Fig. 2). She had never smoked or consumed alcohol,
Figure 1. A chest CT at preoperative evaluation of thymoma, at 4 months before the first evident infectious episode, revealed a well-margined anterior mass (arrow) with a diameter of 5.3 cm, suggesting thymoma.

Figure 2. Histological findings of the resected mediastinal tumor. Each tumor nest consisted of small lymphocytes (black arrow) and neoplastic epithelial cells (white arrow). Neither of them had marked atypia (Hematoxylin and Eosin staining; original magnification x20). Other areas disclosed a lymphocyte-poor type A thymoma component (data not shown). These findings confirmed the diagnosis of type AB thymoma (WHO classification).

Figure 3. Flow cytometry of peripheral blood of the patient demonstrated lymphocyte consisting of 80% T cells (CD 3 positive, data not shown), 18% natural killer cells (CD 3 and 19 negative, CD 16 and 56 positive; right bottom square) and 0% B cells (CD 3, 16, 19 and 56 negative; left top square). The cell populations presented here were gated for CD3 negative cells. Antibodies used were BD Multitest CD3/CD16 + CD56/CD45/CD19 (catalog #340500), and the results were analyzed with BD FACS Canto Clinical software (both from BD Biosciences, San Jose, CA).

Figure 4. A chest CT on the first evident infectious episode revealed an abscess at the sternum (black arrow), pneumonia at the right upper (not shown) and right lower lobe (white arrow) pneumonia, accompanied by bilateral pleural effusion.

and her family history was noncontributory. Physical examinations on admission to our hospital revealed a fever of 39.6 °C, moist skin, a painful bulge at the anterior chest midline on the incision scar with local pyrexia and hyperemia, and coarse crackles at the right lower chest. Complete blood counts and serum chemistry suggested a serious infectious event with markedly elevated leukocyte count of 32,200/μL with left-shifted hemogram, platelet count of 61.7x10^4/μL, C-reactive protein of 49.5 mg/dL, slight elevation of alkaline phosphatase of 574 U/L (normal <359 U/L), serum creatinine of 0.99 mg/dL and uric acid of 8.4 mg/dL. Significantly decreased levels of IgG (344 mg/dL), IgM (54 mg/dL), IgA (<10 mg/dL) and IgE (<8 IU/mL) were also noted. Evaluation of peripheral lymphocytes by flow cytometry revealed a lack of B cell lineage (positive for CD19 and negative for CD3, 16 and 56, Fig. 3). Antibody to human immunodeficiency virus was negative. Urinalysis and electrocardiogram were normal. A chest X-ray and CT scan revealed infiltration in right upper and lower lobes, a mass at the sternum and anterior mediastinum, and bilateral pleural effusion (Fig. 4). Culture of drained fluid by mediastinotomy yielded Streptococcus pneumoniae, establishing a diagnosis
Table 1. Infectious Episodes Requiring Hospitalization

<table>
<thead>
<tr>
<th>Timing*1</th>
<th>Duration of Hospitalization</th>
<th>Infectious Disease</th>
<th>Sites of Disease*2</th>
<th>Pathogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 3</td>
<td>113 days</td>
<td>Mediastinitis/Pneumonia</td>
<td>Mediastinum: RUL, RLL</td>
<td>Streptococcus Pneumoniae</td>
</tr>
<tr>
<td>Month 9</td>
<td>10 days</td>
<td>Pneumonia</td>
<td>RLL, LLL</td>
<td>Haemophilus Influenzae</td>
</tr>
<tr>
<td>Month 42</td>
<td>15 days</td>
<td>Pneumonia</td>
<td>RML, RLL</td>
<td>Bacterial (suspected)</td>
</tr>
<tr>
<td>Month 45</td>
<td>18 days</td>
<td>Pneumonia</td>
<td>LUL, LLL</td>
<td>Bacterial (suspected)</td>
</tr>
<tr>
<td>Month 62</td>
<td>19 days</td>
<td>Pneumonia</td>
<td>Diffuse</td>
<td>Streptococcus Pneumoniae</td>
</tr>
</tbody>
</table>

*1 Timing from thymectomy
*2 Episode of the first admission
* RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe

Discussion

The present patient was characterized by repeated bacterial infectious episodes, in particular respiratory infections, and severe hypogammaglobulinemia with severe deficiency in B lymphocytes after resection of thymoma. These clinical manifestations are concordant with Good syndrome associated with thymoma. This condition affects both genders equally (with a man to woman ratio of 24 to 27), and the mean age of reported patients is 56 (ranging from 29 to 75) years old. Out of 51 patients, thymoma and hypogammaglobulinemia was initially diagnosed in 18 (35.3%), and 23 (45.1%) patients, respectively. In the other 10 (19.6%) patients, both were diagnosed simultaneously (5).

Although immunoglobulin was not evaluated pre- or perioperatively, severe hypogammaglobulinemia was confirmed twice, at 3 months and again at 6 years after thymectomy. In addition, a lack of B cell lymphocyte lineage was demonstrated by flow cytometry of circulating peripheral blood. A similar case with complete disappearance of B cell lineage in the peripheral blood was reported previously (8). Such flow cytometric findings in the peripheral blood do not imply total disappearance of B cells. B cells might exist in the spleen, lymph nodes and other lymphatic apparatus in the lung and intestine, assuring immunoglobulin productions, although significantly inhibited.

Similar to Good syndrome, some paraneoplastic syndromes are caused by autoimmunity against common antigens between tumor cells and target cells or biological molecules. In some of these syndromes, clinical manifestations are often resolved by means of tumor removal or shrinkage. Examples for these include Lambert-Eaton myasthenic syndrome associated with small-cell lung cancer (9) and myasthenia gravis associated with thymoma (10). In contrast, Good syndrome associated with thymoma, in general, is not resolved by treatment of the thymoma (2, 5). In fact, previous reports of this syndrome state that the clinical manifestations last for years, including a patient suffering from this condition for as long as 9 years (2). The underlying mechanism of sustainability of this condition after resecting thymoma is not understood. First of all, the precise mechanism of Good syndrome itself has never been under-
stood, with the exception of some speculations. These include possibilities of disturbance in B cell lineage differentiation due to putative bone marrow-derived humoral factors (7), and T cell dysfunction causing disturbed B cell lineage differentiation (11). In the latter hypothesis, this kind of T cell dysfunction possibly causes both thymoma and hypogammaglobulinemia, and may explain the sustainability of Good syndrome after thymectomy (12).

Durable and severe hypogammaglobulinemia certainly causes repeated infections and, in extreme cases, the outcome may be lethal. In fact, a review of the literature revealed that 29 out of the 51 previously reported patients (57%) with Good syndrome had died due to infectious diseases with a mean follow-up period of 1.5 years (ranging from a few days to 9 years) (5). The present patient also encountered several episodes of infectious diseases, the most serious being the first episode of mediastinitis that required mediastinal drainage with mediastinotomy and antibiotic therapy for as long as 3 months. The most recent episode was also serious because she had diffuse pneumonia in bilateral sides. Treatment with antibiotics supplemented by intravenous immunoglobulins was successful in resolving this serious condition in a relatively short period. Immunoglobulin supplementation for patients with infectious diseases associated with Good syndrome is reasonable, and has as a matter of fact been recommended by multiple expert panels (13).

Thymoma is generally characterized by a low-grade malignant phenotype, and complete resection of the tumor very often leads to a cure of the disease. The concomitant presence of Good syndrome with thymoma, therefore, should be carefully monitored and treated as soon as possible when infections are presented. Clinicians should be aware of this condition, and serum immunoglobulin levels should be evaluated when patients with thymoma are suspected to be vulnerable to infection.

References


© 2009 The Japanese Society of Internal Medicine
http://www.naika.or.jp/imindex.html