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CASE REPORT

Intravenous immunoglobulin replacement therapy to prevent pulmonary infection in a patient with Good's syndrome

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Good's syndrome is an acquired immunodeficiency state associated with thymoma and characterized by recurrent pulmonary infections. We describe a 67-year-old woman who presented with respiratory symptoms caused by concomitant disseminated cytomegalovirus infection and *Pneumocystis jiroveci* pneumonia 38 months after thymectomy for a thymoma. Immunologic analysis revealed hypogammaglobulinemia with absent B-cell population as demonstrated by flow cytometry, consistent with Good's syndrome. Following treatment with sulfamethoxazole/trimethoprim and ganciclovir, the patient improved with resolution of her respiratory symptoms. However, the patient subsequently experienced additional infections, necessitating additional subsequent hospital admissions. During the last admission, intravenous immunoglobulin (IVIG) replacement therapy was initiated and continued after discharge.

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Infection has been prevented for one year after beginning IVIG replacement therapy. This case reveals that in patients with combined humoral and cell-mediated immune deficiency, concomitant infection with different pathogens is not unusual, and immediate specific therapy is important. Periodic IVIG infusion, to maintain adequate Ig levels, is recommended.

Introduction

Patients with thymoma can experience various forms of paraneoplastic syndromes. The three most common are myasthenia gravis, pure red cell aplasia, and hypogammaglobulinemia.[1] Hypogammaglobulinemia occurs in 3–6% of patients with thymoma. This association, first reported by Robert Good and colleagues in 1954, is referred to as Good's syndrome,[2] and is characterized by low to absent B-cell numbers in the peripheral blood, hypogammaglobulinemia, and defects in cell-mediated immunity, resulting in recurrent infection by various microbial pathogens. We herein present the successful treatment of a patient with Good's syndrome infected with concomitant disseminated cytomegalovirus (CMV) infection and *Pneumocystis jiroveci* pneumonia (PJP), and discuss the use of prophylactic immunoglobulin replacement therapy for such patients.

Case report

A 67-year-old woman was admitted to our hospital because of dyspnea and fever for 1 day. She had been in good health until 6 years earlier, when she started to experience a refractory productive cough. At that time, chest computed tomography performed showed a heterogeneous soft-tissue mass (approximately 13.8 × 9.5 × 6.0 cm) in the prevascular space of the left anterior mediastinum, consistent with a thymoma (Fig. 1). Thymectomy was performed through a median sternotomy. Histopathological diagnosis of the resected tumor was consistent with a thymoma, type AB, based on the World Health Organization classification. The tumor had infiltrated into, but not through, the capsule. She received adjuvant radiation therapy after the operation. Following completion of the therapy, the patient remained in good health until 3 months after the operation, when she was admitted for PJP and herpes zoster infection of the skin. She was subsequently admitted to the hospital twice due to sepsis by *Streptococcus pneumoniae* and CMV infection on the 27th and 35th months. Thirty-eight months after thymectomy, she was admitted again. Physical examination on admission revealed a fever of 39.6 °C, pulse rate 116 bpm, blood pressure 92/60, respiratory rate 28, and SpO_2: 96% under 3 L/min nasal canula, moist skin, and coarse crackles in the bilateral lower chest. The leukocyte count was 13,240/μL with 86% neutrophils, 9% bands, a platelet count of 230,000/μL, and a C-reactive protein level of 10.38 mg/dL. Arterial blood gas showed a pH of 7.39, $PaCO_2$ of 44 mmHg, PaO_2 of 75 mmHg, and SaO_2 of 96% while breathing 60% supplemental oxygen via a face mask. Chest computed tomography on admission showed diffuse reticulonodular/ground-glass opacities and interstitial infiltration bilaterally, suggestive of chronic interstitial lung disease with superimposed acute infection (Fig. 2). Broad-spectrum antibiotic treatment with piperacillin/tazobactam was administered. Since her medical history indicated repeated episodes of pneumonia with various pathogens, including opportunistic pathogens, the immune status of the patient was assessed during the hospitalization. Significantly decreased levels of IgG (375 mg/dL), IgM (5 mg/dL), IgA (38 mg/dL), and IgE (<5 IU/mL) were noted. Evaluation of peripheral lymphocytes by flow cytometry revealed the lack of B-cell lineage (negative for CD19 and positive for CD3) with reversed T helper to suppressor ratio (0.32). CD4 T-cell number was 452/μL. Antibody to human immunodeficiency virus (HIV) was negative. Combined with the previous thymoma history and immune abnormality, these results established a diagnosis of Good's syndrome.

Despite treatment with broad-spectrum antibiotics, the fever persisted with little improvement of the symptoms. Polymerase chain reaction (PCR) using real-time *TaqMan* PCR on blood, urine, and sputum specimens were positive for CMV, consistent with a diagnosis of disseminated CMV infection. The concomitant diagnosis of PJP was established by a positive sputum PCR for *P. jiroveci*. Sulfamethoxazole/trimethoprim and ganciclovir were prescribed accordingly, and symptoms improved after treatment. The patient was then discharged in stable condition, but

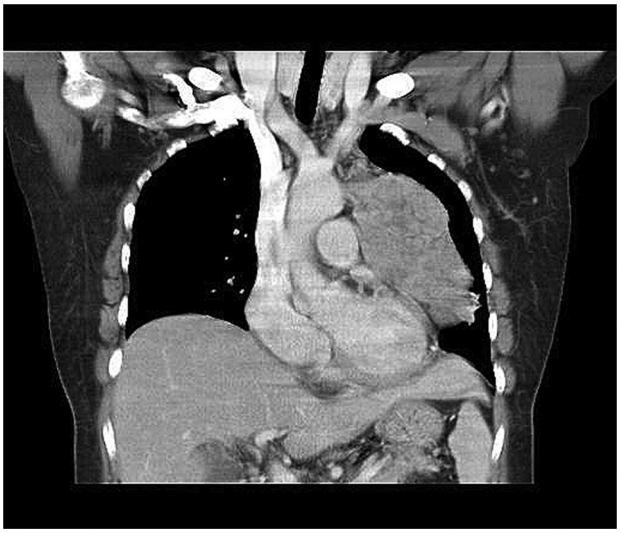

Figure 1. A mass (about 13.8 × 9.5 × 6.0 cm) in the prevascular space of the left anterior mediastinum consistent with a thymoma.

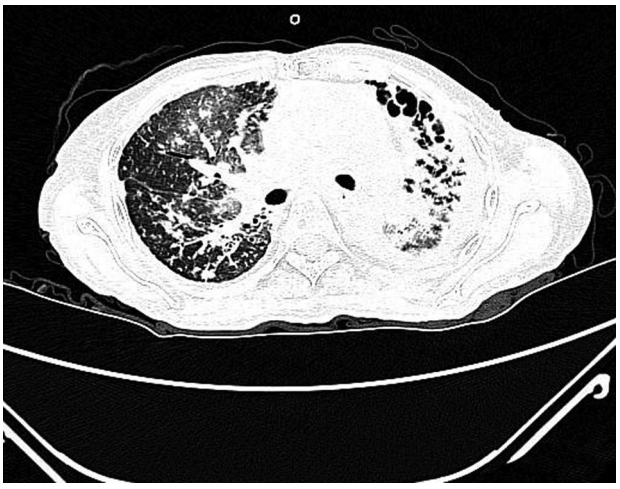

Figure 2. Patchy fibrotic lesions with traction bronchiectasis in both upper lung fields, with destruction and multiple blebs.

experienced another episode of infection (Table 1) necessitating additional hospital admissions. To prevent recurrent pulmonary infections and sequela of impaired lung function, she was begun on intravenous immunoglobulin (IVIG) infusions at 500 mg/kg per day for 5 days. IVIG therapy was continued periodically at an outpatient basis to maintain adequate immunoglobulin levels. Infection has not recurred for 1 year after the start of regular IVIG replacement therapy. The numerous episodes of serious infections requiring hospitalization, all of which occurred before the initiation of Ig replacement therapy, are listed in Table 1. The patient continues to receive regular IVIG supplementation and infection surveillance every 3 months. In the 1-year follow-up after initiating periodic IVIG replacement, this regimen appears to be effective in preventing subsequent infections, although further studies will be required to validate this therapy.

Discussion

Good's syndrome (immunodeficiency with concomitant thymoma) is a combined humoral and cellular immunodeficiency that is now classified as an entity separate from common variable immune deficiency (CVID).[3] Good's syndrome typically occurs in the 4th or 5th decade of life, preceding or following the diagnosis of a thymoma,[2] and is seen with equal frequency in men and women. In contrast to other paraneoplastic syndromes associated with thymoma, the immunologic abnormalities of Good's syndrome are not corrected by corticosteroid treatment or thymectomy.[4]

The main characteristics of Good's syndrome are hypogammaglobulinemia due to a low or absent B cell count and variable defects in cell-mediated immunity, an abnormal CD4+/CD8+ T cell ratio, and an impaired T-cell mitogenic response. However, the underlying pathogenesis of Good's syndrome remains unclear. At least two possible pathogenic mechanisms have been proposed. The first potential mechanism is that cytokines, possibly released by bone marrow stromal cells, inhibit both thymic and B-cell precursor growth and differentiation. The second potential mechanism is suggested by the observation that T cells isolated from patients with thymoma can inhibit both pre-B cell growth and immunoglobulin production by B cells.[5] Since both humoral and cell immunity are compromised, individuals with Good's syndrome are susceptible to various infections, including opportunistic viral, bacterial, and fungal infections.

Tarr et al[2] reported that sinopulmonary infection with *Haemophilus influenzae* was the most common infectious disease among 51 patients with immunodeficiency and thymoma. Other infections observed in their patients were CMV, PJP, infectious diarrhea, and tuberculosis.[2] Our patient had a history of recurrent pneumonia caused by bacterial, fungal, and viral pathogens, suggestive of immunocompromised status. Low levels of immunoglobulin and lack of B cell lineage by flow cytometry confirmed the diagnosis of Good's syndrome. The interstitial pneumonitis improved after treatment with sulfamethoxazole/trimethoprim and ganciclovir for concurrent PJP and CMV infections. Follow-up chest high-resolution computed tomography, performed 3 months after discharge, showed bronchiectasis and interstitial lung disease, consistent with prior lung injury from prior recurrent infections.

Adequate replacement of immunoglobulin has been shown to reduce the incidence of pneumonia in CVID.[6] The efficacy of this therapy has not been validated for

Table 1 Infectious episodes requiring hospitalization

Time after thymectomy (mo)	Duration of hospitalization	Infectious disease	Pathogen
3th	28	Pneumonia	*Pneumocystis jiroveci*
27th	7	Pneumonia with sepsis	*Streptococcus pneumoniae*
35th	13	Pneumonia and CMV viremia with sepsis	CMV
38th[a]	16	Pneumonia and CMV viremia with sepsis	*P. jiroveci* and CMV (PCR in blood, urine, sputum)
41th	6	Pneumonia	Unspecified bacteria
46th	7	Pneumonia and CMV viremia with sepsis	CMV
48th	36	Pneumonia with acute respiratory failure	*P. jiroveci* and CMV
53th[b]	10	Pneumonia	Unspecified bacteria

[a] Good's syndrome was diagnosed at this admission.
[b] Intravenous immunoglobulin replacement therapy started at this admission.

Good's syndrome, although some retrospective data would support such a regimen.[4] Since Good's syndrome is similar to CVID with regard to immune abnormality, we hypothesized that Good's syndrome might also benefit from IVIG therapy. Therefore, the patient was administered IVIG infusions to maintain serum IgG levels of at least 500 mg/dL, as for patients with CVID, along with surveillance for signs of infection. Since the initiation of periodic IVIG replacement therapy, further infections have been prevented.

Previous reports revealed that both humoral and cell-mediated immunity are critical for the control of CMV infections.[7,8] Preemptive treatment for CMV viraemia has been documented to prevent CMV disease in solid organ transplant recipients.[9] Although we are not aware of any reports of the treatment of disseminated CMV infection in Good's syndrome, we aggressively treated our patient for disseminated CMV infection since patients with Good's syndrome are also severely immunocompromised, similar to that seen in solid organ transplant recipients.

P. jiroveci can cause a lung infection in people with impaired immunity, especially in people with cancer, individuals with AIDS, and users of immunosuppressive medications. While it is not surprising that a patient with Good's syndrome presented with PJP, few such case reports have been described.[2] In non-HIV immunocompromised patients (specifically, adults with acute leukemia or solid organ transplantation), prophylaxis for PJP with trimethoprim/sulfamethoxazole, an antibiotic effective against PJP, significantly reduced the occurrence of PJP by more than 90%.[10] It is still uncertain whether other Good's syndrome patients could benefit from such a prophylaxis regimen.

Our case reveals that in adults with a history of a thymoma who present with recurrent pulmonary infections, Good's syndrome should be taken into consideration. As demonstrated by our patient's medical history of recurrent infections (Table 1), a patient with Good's syndrome can present with respiratory infections caused by a wide range of pathogens, including opportunistic pathogens. In addition to immediate treatment of the specific infection with appropriate antimicrobial agents, chronic IVIG replacement should be considered to prevent recurrent infections although further studies will be needed to validate the benefit of this therapy.

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