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Case Report Open Access

Good's Syndrome: A Case with Recurrent Respiratory Infections and a Brief Review of the Literature

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Abstract

Background: Thymomas are tumors associated with autoimmune disorders like myasthenia gravis, Pure Red Cell Aplasia (PRCA), and acquired hypogammaglobulinemia (Good's syndrome). The failure of thymomas to express autoimmune regulator has been shown to be a potential contributing factor to autoimmunity.

Case report: A 78-year old man with recurrent sinopulmonary infections, and megaloblastic anemia diagnosed PRCA by bone marrow aspiration. Further investigation revealed thymoma associated acquired hypogammaglobulinemia. Thymectomy failed to resolve PRCA, and the patient was commenced on periodic Intravenous Immunglobulin (IVIG) therapy for both to achieve improvement of PRCA and to support humoral immunity. On IVIG therapy the frequency of respiratory infections decreased significantly. The patient was also given prophylaxis against herpes viruses, and *Pneumocystis jiroveci*, and got vaccination for capsulated bacteria. As the trial of IVIG therapy had no effect on PRCA he was started oral corticosteroid treatment. PRCA resolved and steroid therapy was tapered gradually. He has been on remission for nine years without requirement of systemic steroid. The case is a very rare kind of it's in the literature.

Conclusion: The clinical experience on management of Good's syndrome and PRCA by steroid therapy and regular IVIG infusions, and also the use of prophylactic agents and immunization against opportunistic infections was underlined here. The careful monitoring for any signs of oncoming respiratory infection and early intervention has utmost importance for this special group of patients.

Keywords: Thymoma; Hypogammaglobulinemia; Pure red cell aplasia

Introduction

The role of the normal thymus in establishing the development of a normal immune system is still being investigated. The progenitor cells that leave bone marrow migrate to the thymus where they differentiate into mature T lymphocytes. In their sequence of differentiation those that are potentially auto reactive are deleted in the medulla by dendritic cells against major histocompatibility complex antigens and by medullary thymic epithelial cells against tissue-restricted antigens. The Autoimmune Regulator (AIRE) promotes expression of peripheral tissue-restricted antigens such as insulin by medullary thymic epithelial cells and induction of tolerance to them. The failure of thymomas to express autoimmune regulator has been shown to be a potential contributing factor to autoimmunity [1]. Approximately 40% of thymomas are associated with different paraneoplastic syndromes, of which MG, PRCA, and hypogammaglobulinemia are the most clinically important ones. Thymoma associated with hypogammaglobulinemia was first reported by Dr Robert Good in 1954, after whom it was named as Good's syndrome [2-4]. Good's syndrome is characterized by hypogammaglobulinemia, depleted B cells, diminished T cells, and the inversion of the $CD4^+/CD8^+$ ratio [3-6]. The full-blown clinical spectrum was observed in our case, with recurrent sinopulmonary infections reflecting immunodeficiency.

Case Report

A 78 year-old man was followed regularly by our clinic since we diagnosed Good's syndrome.

On history, he had been healthy until 9 years earlier when he experienced frequent symptoms suggestive of respiratory infection. He was given several antibiotics by his primary physician on his attacks of fever with purulent sputum formation. Routine chest radiographies had been unrevealing at that time.

A complete blood count revealed macrocytic anemia, with a hemoglobin level of 8.3 g/dL, a hematocrit of 22%, a mean corpuscular volume of 10^4 fL, a mean corpuscular hemoglobin of 35.6 pg/dL, and the leucocyte and platelet counts were normal. He was referred to hematology for further investigation of megaloblastic anemia. A bone-marrow aspirate specimen showed normal granulopoiesis, normal megakaryopoiesis and the complete absence of erythroid precursors. The bone marrow biopsy also reported normal myeloid series, and the absence of erythroid progenitor cells compatible with PRCA. Acquired

PRCA led to the possibility of thymoma. The contrast-enhanced computed tomography scan detected a homogenously enhanced, regular contoured 2.5 × 2.5 cm anterior mediastinal mass located at anterior neighbourhood of the main pulmonary artery. The thymoma was diagnosed, and a thymectomy was carried out via partial median sternotomy. The pathological examination identified a lymphoepithelial thymoma, and diagnosis of thymoma-associated PRCA was confirmed. The patient was given radiotherapy following surgery.

Thymectomy had no effect on PRCA, and the patient required multiple blood transfusions. Intravenous immunoglobulin at a dose of 0.5g/kg/d for 5 days was ineffective for PRCA as well. He lastly recieved systemic (oral) steroid (Prednol, 1 mg/kg/day). PRCA recovered, and hemoglobin increased to 13.2 g/dL. Steroid was tapered slowly in six months. He experienced no relapse thereafter.

The serum immunoglobulin levels were shown at Table 1.

	Patient	Normal range
IgG (mg/dL)	578	800-1.808
IgA (mg/dL)	30.7	90-453
IgM (mg/dL)	5.26	60-350

Table 1: The levels of immunoglobulins

Evaluation of peripheral lymphocytes by flow cytometry demonstrated an inverted $CD4^+$:$CD8^+$ T cell ratio (0.17), 92 % T cells ($CD3^+$), 17% natural killer cells (CD3- and 19-, $CD16^+$ and 56^+), and 0% B cells ($CD19^+$ and $CD3^-$, 16^-, and 56^-).

During follow-up the patient developed an attack of respiratory infection again. The chest radiography showed no localized infiltration suggestive of lobar pneumonia, but diffuses ground-glass opacities with variable hyperinflation areas (Figure 1). The attack was responsive to 2-weeks oral levofloxacin therapy.

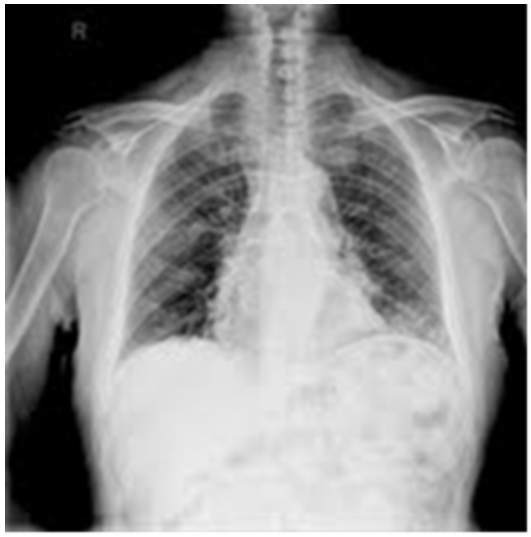

Figure 1: Diffuse ground-glass opacities with hyperinflation areas.

We offered this patient oral acyclovir prophylaxis (Zovirax ,400 mg twice dailly) against Herpes viruses, and prophylaxis against Pneumocystis jiroveci by trimetophrim/sulfamethoxazole (Bactrim, 160/800 mg oral daily). He got vaccination for encapsulated bacteria as well.

Without any serious infectious attacks requiring hospitalization, the patient has been followed up for more than 9 years with 21-days-interval administrations of IVIG.

Discussion

The presented case illustrates a rare case of both PRCA and GS simultaneously occurring in a patient with thymoma. This is an extremely rare, acquired condition of adults, characterized by thymoma, hypogammaglobulinemia, and low number of peripheral B cells, and acquired anemia. After a durable period of hypogammaglobulinemia of almost 8 years the full syndrome was established, characterized by chronic sinopulmonary infections, and development of bronchiectasis in this patient.

Thymoma is a neoplasm originating from the thymic epithelium and approximately 40% of thymoma patients have clinically associated paraneoplastic syndromes including MG, PRCA, hypogammaglobulinemia (Good's syndrome), autoimmune disorders and vasculitis. The incidences of PRCA, and hypogamaglobulinemia in thymoma patients are reported to be 1.6-5%, and 3-6%, respectively [2,3].

Thymothymectomy should be performed to avoid local invasion, dissemination and metastatic spread of thymoma. However, thymothymectomy does not restore immune function in almost all cases. By consensus, standard immunoglobulin replacement is useful for hypogammaglobulinemia. A retrospective review of the efficacy of immunoglobulin replacement for Good's syndrome showed that 23 of 30 patients had favorable responses during their follow-up periods [4]. However, there are no other established treatment options to suppress infections.

The most common infectious complication of Good's syndrome is recurrent sinopulmonary infections as in this case, and mostly due to encapsulated bacteria. According to the study by Tarr et al the infections most commonly observed in the patients with Good's syndrome so far included recurrent sinopulmonary infections, generally with encapsulated bacteria, most often Haemophilus influenzae, followed by mucocutaneous *candida* infections, and Cytomegalovirus (CMV) disease [4]. In our patient the history was suggestive of CMV ulcers in tongue accompanied by retinitis, although it was not clarified exactly by tissue sampling and/or laboratory investigations. Clinically significant CMV disease and other opportunistic infections appear to develop more frequently in Good's syndrome patients than other hypogammaglobulinemic conditions [5,6]. This suggests that there have been severe cellular immune defects in these patients as well, and was supported by in vitro studies that showed defects in T lymphocyte proliferation and/or Interleulin-2 (IL-2) production in these patients [6]. The immunodeficient state of the patient was thought to be responsible for both recurrent respiratory infections and activation of latent infections.

There has been no standard treatment of Good's syndrome with PRCA as the condition is very rare. Surgical resection of thymoma without any additional treatment resolves PRCA in about 30% of cases. Immunosuppressive therapy may be necessary to achieve

complete remission in case of PRCA. But controversies exist about use of immunosuppresives because of accompanying deficient humoral immunity. Therefore in such case of PRCA associated with hypogammaglobulinemia standart immunoglobulin replacement is useful for both to achieve resolution of PRCA and to suppress infections [4-6]. The most common infections are recurrent respiratory infections by encapsulated organisms, such as *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Neisseria meningitidis*. Vaccination against these microorganismms should be warranted in each case also.

In our case PRCA did not improve after surgery or by IVIG administrations. Frequent blood transfusions were required. We achieved complete resolution of PRCA with administration of systemic steroid that was tapered slowly within six months, and no relapses were observed from then on. Good's syndrome did not respond to either surgical resection or immunusuppressive treatment in our patient as typically observed with previous reports. However, with monthly intravenous immunoglobulin supplementation of 0.5 g/kg the rate of respiratory infections decreased.

In conclusion, thymoma associated PRCA accompanied by Good's syndrome deserves great attention regarding the treatment strategy targeted both to PRCA and to infectious complications. We recommend that a careful management with intensive infection-control using antibiotics and intravenous immunoglobulins is required for the long term. We also recommend vaccination against encapsulated microorganisms, and prophylaxis for herpes simplex virus infection and *Pneumocystis jiroveci* as a part of the management. The decision of immunosuppressive therapy for PRCA is to be established by investigations with larger numbers of cases.

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