Good's syndrome, a rare form of acquired immunodeficiency associated with thymomas

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Abstract

Good's syndrome (GS) or thymoma-associated immunodeficiency is a rare clinical entity that should be ruled out in patients with thymoma who develop severe, recurrent bacterial infections and opportunistic viral and fungal infections. There are no treatment protocols established, hence, early recognition is imperative to avoid complications. We report the case of a 42-year-old female, known for a previous thymectomy for giant thymoma who has suffered for a long time from recurrent pulmonary and urinary tract infections and cold sores. In March 2016 she referred to our unit complaining of fever, cough, chest pain, and cold sores due to *Herpes simplex* virus (HSV), confirmed serologically as HSV-1. Chest X-ray showed left pneumonia due to *Streptococcus pneumoniae*. She started antibiotics (amoxicillin/clavulanic acid associated with azithromycin) with gradual improvement. Given her history she was studied for an underlying immunodeficiency: IgG, IgA, and IgM were significantly low or absent, as well as all IgG subclasses; blood and bone marrow aspirate leucocyte immunophenotyping showed complete absence of B lymphocytes and reduced CD4+ T cells. In light of: i) thymoma; ii) B lymphocyte deficit; iii) hypogammaglobulinemia; iv) recurrent infections, GS was diagnosed and pre-emptive immunoglobulin treatment, associated with HSV and *Pneumocystis jiroveci* prophylaxis (Acyclovir for HSV and Sulfamethoxazole-Trimethoprim for *P. jiroveci*) were started. Since then the patient has no longer presented any infectious episodes.

Introduction

Thymoma is an uncommon and slow-growing thymic epithelial, a rare malignancy that arises from the epithelium of the thymic gland. While half of the patients are asymptomatic, the other half present with mass-effect and chest related symptoms such as dyspnea and chest pain. Thymomas should be associated with myasthenia gravis, autoimmune disorders like systemic lupus erythematosus and rheumatoid arthritis, hematologic syndromes and other chronic diseases such as hypertension, diabetes mellitus, renal insufficiency and coronary artery disease. A history of second tumor may be present in some patients. Finally it should be found incidentally. Parathymic syndromes include myasthenia gravis, pure red cell aplasia, connective tissue disorders and acquired hypogammaglobulinemia or Good's syndrome (GS). This clinical entity should be ruled out in patients with thymoma who develop severe, recurrent opportunistic infections.[1] GS was first reported by Robert Good in 1954 and it is usually characterized by thymoma, hypogammaglobulinemia, low or absent B-cells, decreased T-cells, an inverted CD4+/CD8+ T-cell ratio and reduced T-cell mitogen proliferative responses.[2] GS has no well established therapeutic schedule and the diagnosis can be difficult; thymectomy and immunoglobulin replacement treatment have become the major management approaches. Although rare, this relentless syndrome needs to be promptly identified so that pre-emptive treatments can be started. The signs and symptoms a patient presents with may not appear initially interrelated. GS can be easily missed especially because of its protean manifestations of autoimmune and parathymic syndromes. It is crucial that, once a diagnosis of thymoma is made, clinicians collect a thorough history and make in-depth evaluations, with longitudinal follow-up and surveillance to rule out the composite spectrum of manifestations associated with this condition. Immunoglobulin replacement has been reported to improve outcome by reducing the infection rate in patients with GS[3,4] and associated hypogammaglobulinemia.

Case Report

We report the case of a 42-year-old Caucasian female, working as a teacher. During the previous ten years she had suffered from airway infections: recurrent bronchitis and bacterial pneumonia, approximately 4 episodes a year. The patient also had a 10-year history of cyclical cold sores due to *Herpes simplex* virus (HSV) – in the past also confirmed by swab test – and recurrent urinary infections.

In 2011, she showed persistent cough and modest wheezing and for this performed a chest X-ray that displayed a mediastinum widening. Subsequent chest computed tomography (CT) surveys suggests the presence of a thymoma and therefore she underwent thymectomy for a giant thymoma: Figure 1 displays the CT scan at diagnosis and Figure 2 shows the typical lymphoid infiltrate at histological analysis.

In March 2016, the patient referred to our Emergency Department complaining fever, persistent cough and chest pain that developed during a recent bronchitis and that had been treated with levofloxacin; a previous chest X-ray was negative. She also had cold sores in the vesicular phase (Figure 3). Initially blood chemistry and acute-phase reactants were normal, but a subsequent chest X-ray evidenced a left basal pneumonia. The patient was admitted with the diagnosis of pneumonia and tested for common opportunistic infections and Pneumococcal and Legionella urinary and blood tests were done, too. A positive Pneumococcal urinary antigen test and positive blood culture for *Streptococcus pneumoniae* were documented. An antibiotic treatment with amoxicillin/clavulanic acid associated with azithromycin was started,

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with gradual reduction of fever and complete recovery of symptoms.

Given the history of thymectomy, recurrent infections, and *Herpes labialis*, the patient was studied for immunodeficiency causes: seroprotein electrophoresis showed severe hypogammaglobulinemia and serum IgG, IgA, and IgM were significantly low (144 mg/dL [r.l. 690-1400 mg/dL], 11 mg/dL [70-400 mg/dL], 2 mg/dL [r.l. 40-230 mg/dL], respectively), as well as all IgG subclasses (IgG1 1.03 g/L [reference levels 4-13 mg/dL]; IgG2 062 g/L [r.l. 1-6 mg/dL]; IgG3 0.04 g/L [r.l. 0.2-1.7 mg/dL]; IgG4 0.01 g/L [r.l. 0.04-2.3 mg/dL]). Peripheral blood lymphocyte count was low (600/mL), the lymphocyte immunophenotyping showed the total absence of CD19+/CD20+ B cells, and a reduced TCD4+ percent and absolute count (31% and 186/mL, respectively) with a CD4/CD8 ratio of 0.68 (Figure 4). On the other hand immunofixation was negative and urine Bence Jones Protein absent. The bone marrow aspirate analysis showed a reactive pattern with hemophagocytosis and confirmed the complete absence of B lymphocytes. HIV test was negative. Low-resolution HLA typing of locus A, B and D-DR did not disclose any significant disease-related alleles.

The clinical conclusion took into account the previous medical history and: i) previous thymoma, ii) B and CD4+T lymphocyte absence or deficit, iii) severe hypogammaglobulinemia, iv) recurrent infections, so that a diagnosis of GS was made.

A pre-emptive treatment with intravenous immunoglobulins[3] associated with HSV and *Pneumocystis jiroveci* prophylaxis (Acyclovir 400 mg 3 times a week for HSV and Sulfamethoxazole-Trimethoprim 800/160 mg 3 times a week too for *P. jiroveci*) were started and, since then, the patient remained in a stable health status, with no further infectious episodes recorded. Her immunological status remains stable during the last two years, as shown in Figure 5 and in Tables 1 and 2.

Discussion

Although rare, GS needs to be promptly identified so that the appropriate treatment can be started. This condition should be suspected in hypogammaglobulinemia associated with the presence of thymoma but in the same way in hypogammaglobulinemia of unknown aetiology the possible presence of thymoma should always be investigated. Thymoma is best known for its association with myasthenia gravis, but it is also associated with other pathological conditions, like GS. Patients with GS typically have hypogammaglobulinemia and a reduced B cell and CD4+ T cell count. The usual clinical presentation is determined by the underlying immunodeficiency. This affects both humoral and cellular components. The diagnosis is based on clinical criteria. Our patient – already known for a previous removal of giant thymoma – reported a long story of repeated sinopulmonary bacterial infections, chronic diarrhea, urinary tract

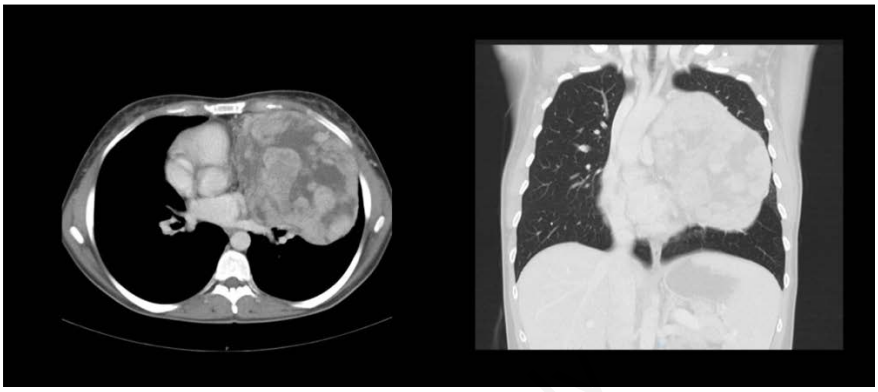

Figure 1. Chest computed tomography scan image depicting massive thymoma, which was then surgically resected with efficacy.

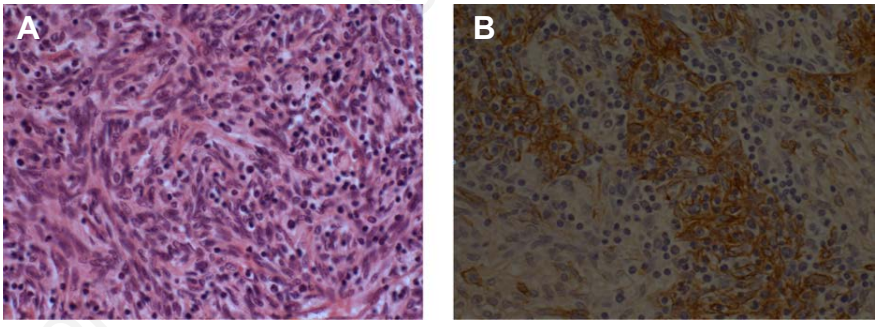

Figure 2. Histological section of thymoma. A) Red blood cells, large frustules of rather monomorphic fused elements in small lymphocytes. Framework compatible with thymoma. Hematoxylin eosine coloring 40× magnification. B) Focal macrophagic areas and thickened reticulin plot surrounding both groups and single cells. Cytokeratin coloring 40× magnification.

Table 1. Patient's immunoglobulins absolute values before and after the treatment.

	Reference range	April 16, 2007	June 24, 2015	June 3, 2016
IgG	690-1400 mg/dL	334	144	508
IgA	70-400 mg/dL	332	11	6
IgM	40-230 mg/dL	5	2	6

Table 2. Results of the immunological work-up were not contributory except for reduced total gamma globulins.

Patient's immunologic work-up during hospitalization	
ANA	1:80
ENA	Negative
ANTI dsDNA	Negative
γ-globulins	1.8 gr/dL

ANA, anti-nuclear antibodies; ENA, extractable nuclear antigens; ANTI dsDNA, Anti-double stranded DNA antibodies.

infection, peripheral lymphocytopenia associated with persistent hypogammaglobulinemia, absence of peripheral and bone marrow B cells, low CD4+T cell counts, all consistent with the diagnosis of GS.[5-7] For this reason hypogammaglobulinemia should be investigated not only periphery but also with bone marrow aspirates and biopsy, paying particular attention to the B lymphocyte compartment which, as indicated above, normally appears depleted.

Chen *et al*. had already described a case of GS associated with abnormality of circuiting lymphocytes, with lower CD4+ T cells percentages, CD4+/CD8+ cells reversed ratio and a subpopulation of peripheral CD4+ T cells had with lower proliferation capacity and a higher expression levels of PD-1. In this study they demonstrated that the serum IFN-γ secreted

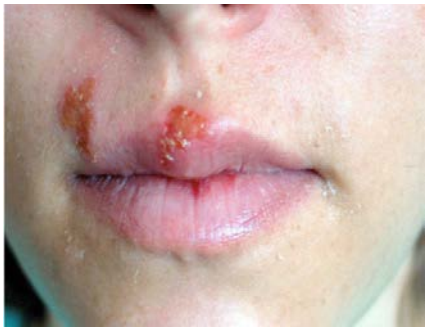

Figure 3. Cold sores due to *Herpes simplex* have been described as a typical clinical manifestation of Good's syndrome. Our patient reported recurrent episodes in her history, confirmed serologically and by swab test.

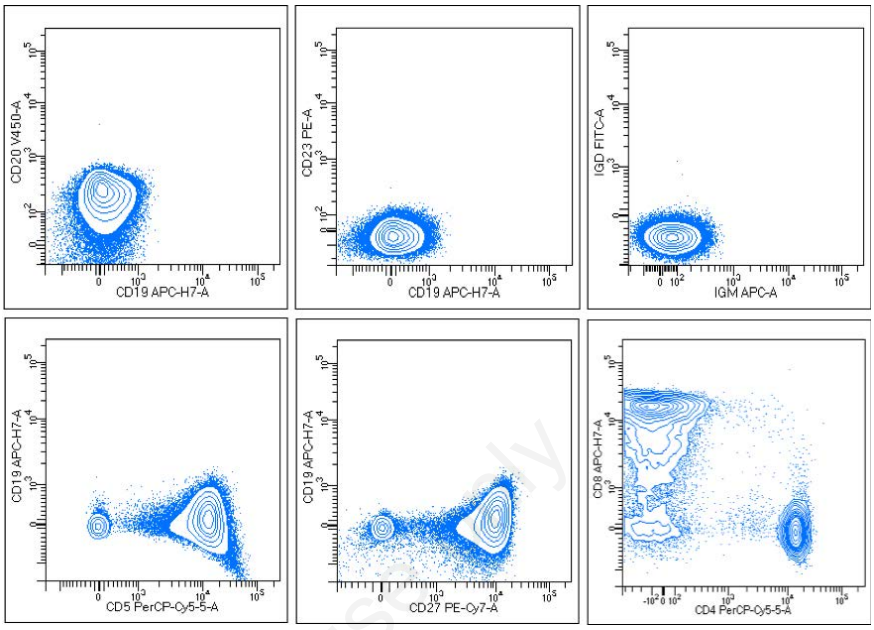

Figure 4. Peripheral blood lymphocyte immunophenotyping. Virtual absence of B cells with preserved T cell subpopulations. NK cells were about 25% of lymphocytes (not shown).

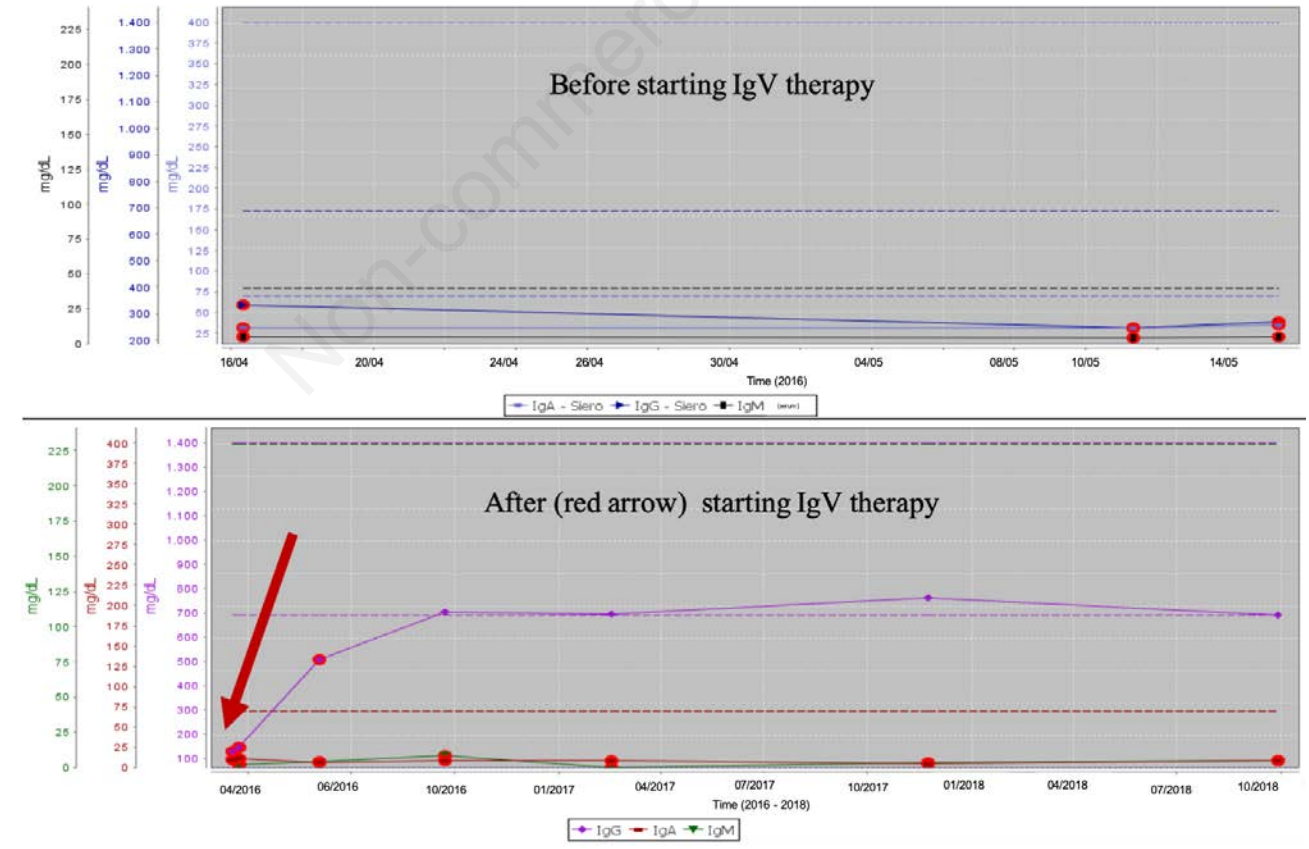

Figure 5. Patient's immunoglobulin trend between 2007 and 2017. Hypogammaglobulinemia persisted with time, with just a slight increase of IgG under treatment.

by γ-δT cells appeared significantly lower in GS patients and the cytokine pattern showed non-specific anomalies (IL-17 pattern) that might explain an increased exposure to pulmonary infections. During infectious episodes, however, neutrophil leucocytosis and increased serum acute-phase reactants are regularly recorded.[8,9]

The patient's recurrent history of diarrhea and sinopulmonary infections (either viral or bacterial) was related to acquired chronic immunodeficiency, not related to HIV infection. The immunodeficiency appeared to affect both humoral and cellular components, predisposing the patient to a spectrum of infections, similar to that which occurs in X-linked agammaglobulinemia (XLA) or in AIDS, but not in common variable immunodeficiency (CVID).[10,11] In contrast to XLA, which occur usually – but not exclusively – in the pediatric population, and CVID – that CVID is more classically primary humoral deficiency – GS is not typical of young people, affects both humoral and cellular components and is characterized by a poor prognosis with a high mortality, about from 44.5% to 57%, in different reviews, mainly because of infectious diseases.

One of the greatest difficulties encountered in the diagnosis of GS is the extreme variety of the symptoms described in the literature: Kelesidis[4] in 2010 described about 19 different autoimmune clinical presentations, from the most common myasthenia gravis to diabetes. We have documented only a non-specific anti-nuclear low titre antibody.

No definite treatment therapy protocol has been established. Treatment must be tailored to the individual patient considering the frequency of infections and measurement of serum antibody levels and CD4+ T-cell count. *P. jiroveci* and HSV prophylaxis is recommended. Use of immunoglobulin replacement has been reported in many case reports to improve outcome by decreasing the infection rate: about 37.5% of patients had decreased infections under such treatment. The U.S. Food and Drug Administration has approved the use of immunoglobulins for the treatment of some kinds of immunodeficiencies; similarly in Italy, IVIg treatment instructions show primitive immunodeficiencies, autoimmune thrombocytopenic purpura, Kawasaki disease, bone marrow transplantation in patients over 20 years, chronic lymphatic leukemia, multiple myeloma, pediatric AIDS, Guillain Barré syndrome. Many other pathologies can be considered but pending of controlled clinical studies because some clinical conditions – such as GS – are rare, making clinical trial implementation extremely difficult. Anyway IVIg replacement should occur in line with formal guidelines and dependent on the absolute value of serum IgG considered with overall infection burden.

Prognosis in patients with GS is thought to be worse than in other immunodeficiencies, hence, early diagnosis is essential to avoid complications that can also be fatal. Therefore, we suggest a diagnostic workup to detect thymoma in patients with hypogammaglobulinemia and decreased peripheral blood lymphocytes: GS should be considered in patients over 40 years of age with otherwise unexplained antibody deficiency.

Finally GS, as is a immunocompromising condition with heterogeneous immune deficits, opportunistic infectious diseases represent a diagnostic and therapeutic challenge, given their protean clinical manifestations.

Preventive guidelines including targeted antimicrobial prophylaxis and vaccination strategies can mitigate infectious complications and prophylactic strategies and vaccinations can be recommended.[12]

Conclusions

In summary, GS is a rare condition whose clinical outcome depends on the severity of infections, and can be influenced by the associated hematologic and autoimmune diseases rather than by the thymoma itself. Although there are still no effective protocols for treating GS, immunoglobulin replacement seems to be the best therapy available.

In conclusion, a multifaceted approach is necessary for the prevention of infectious diseases in patients with GS, including treatment of thymoma and parathymic syndromes, management of hypogammaglobulinemia with immune globulin repletion, employment of targeted antimicrobial prophylaxis, administration of appropriate vaccinations, and adoption of best strategies.

References

1. Dong JP, Gao W, Teng GG, et al. Characteristics of Good's Syndrome in China: a systematic review. Chin Med J 2017;130:1604-9.
2. Good RA. Agammaglobulinemia – a provocative experiment of nature. Bull University Minnesota 1954;26:1-19.
3. Joven MH, Palalay MP, Sonido CY. Case report and literature review on Good's syndrome, a form of acquired immunodeficiency associated with thymomas. Hawaii J Med Public Health 2013;72:56-62.
4. Kelesidis T, Yang O. Review: Good's syndrome remains a mystery after 55 years: a systematic review of the scientific evidence. Clin Immunol 2010;135: 347-63.
5. Kitamura A, Takiguchi Y, Tochigi N, et al. Durable hypogammaglobulinemia associated with thymoma (Good syndrome). Intern Med 2009;48:1749-52.
6. Kelleher P, Misbah SA. What is Good's syndrome? Immunological abnormalities in patients with thymoma. J Clin Pathol 2003;56:12-6.
7. Samson M, Audia S, Lakomy D, et al. Diagnostic strategy for patients with hypogammaglobulinemia in rheumatology. Joint Bone Spine 2011;78:241-5.
8. Granel B, Gayet S, Christides C, et al. Thymoma and hypogammaglobulinemia. Good's syndrome: apropos of a case and review of the literature. Rev Med Interne 1999;20:347-9.
9. Tsai YG, Lai JH, Kuo SY, et al. Thymoma and hypogammaglobulinemia (Good's syndrome): a case report. J Microbiol Immunol Infect 2005;38: 218-20.
10. Notarangelo L. Primary immunodeficiencies. J Allergy Clin Immunol 2010;125:182-94.
11. Primary immunodeficiency diseases. Report of an IUIS Scientific Committee. International Union of Immunological Societies. Clin Exp Immunol 1999;118:1–28.
12. Hagiwara H, Iwata Y, Saito K, et al. Herpes vegetans accompanied by Good's syndrome. J Dermatol 2018;45: e269-71.