

## CASE REPORT

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# Good's Syndrome-Association of the Late Onset Combined Immunodeficiency with Thymoma: Review of Literature and Case Report

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## ABSTRACT

Good's syndrome, the adult onset hypogammaglobulinemia associated with thymoma has been explained about six decades ago. It generally presents with recurrent infections and several paraneoplastic syndromes including myasthenia gravis, pure red cell aplasia, connective tissue disorders, superior vena cava, Horner's syndrome, lichen planus and inflammatory bowel disease. Lack of B cell, dysfunction of T cell, CD4+ T cell lymphopenia, reversed CD4/CD8+ T cell ratio, autoantibodies against Th17 related cytokines have been respected as the pathogenesis of the immune dysregulation this syndrome.

A 57-year-old man was admitted to our hospital with a history of thymectomy due to thymoma (Type A) 6 years ago. He developed weight loss and recurrent persistent diarrhea caused by isospora belli. His chest CT scan revealed bilateral bronchiectasis. His laboratory data showed hypogammaglobulinemia and he was treated by monthly IVIG with the diagnosis of good's syndrome. Nevertheless he referred again with left sided loss of vision because of CMV retinitis and he also developed nail candidiasis.

Good's syndrome should be considered in every patient with a history of thymoma and recurrent infection. Immunologic evaluation of these patients including measurement of the serum level of immunoglobulin as well as B cell and T cell subgroups should be performed. Physicians must be aware and think about this entity in patients with adult onset immunodeficiency.

**Keywords:** Cytomegalovirus; Hypogammaglobulinemia; Retinitis; Thymoma

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## INTRODUCTION

Adult onset hypogammaglobulinemia associated with thymoma was described by Good et al. in 1954 for the first time and is known as Good's syndrome.<sup>1</sup>

Thymomas arise from thymic epithelial cells with an unknown etiology. These are scarce and slow-developing tumors with varying features.<sup>2-4</sup>

Thymomas might express benign or malignant behavior. However, majority of thymomas presented with good's syndrome are benign and 75% are characterized as spindle cell type (type A).<sup>5,6</sup>

General annually incidence of thymoma in the U.S is estimated to be at least 0.13-0.15 per 100,000 people. It is extremely unusual in youngsters and its incidence increases by age to reach the highest level in the 6<sup>th</sup> and 7<sup>th</sup> decades. Thymoma occurs with no genders predominance and the mean age of presentation is not significantly different between male and females. It is more common in Asians probably due to genetic predisposition.

Up to 10% of adult onset hypogammaglobulinemia is attributable to thymoma and hypogammaglobulinemia frequency in thymoma is about 6-11%.<sup>2,3,6,7</sup>

It is associated with lack of B cell and malfunction of T cell that presents with recurring infection and autoimmune manifestations.<sup>8,9</sup> There is no data to support the return of the immune defects to normal after thymectomy.<sup>10</sup>

## CASE REPORT

A 57-year-old man referred to our hospital in 2012 with diffuse bronchiectasis. He had never been smoker or drinker. Family history was negative for recurrent infections or any immunodeficiency.

He underwent thymectomy owing to thymoma (Type A) 6 years ago in the previous hospital. His thymic tissue showed lobular arrangements were made by thick fibrous bands. Each lobule was composed of spindle shaped epithelial cells with vesicular nuclei and inconspicuous nucleoli indicating thymoma type A (Figure 1).

He had also started to develop weight loss and recurrent persistent diarrhea caused by *isospora belli* that was diagnosed by identification of the oocyst through examining a stool sample under a microscope. His diarrhea was responsive to co-trimoxazole so long

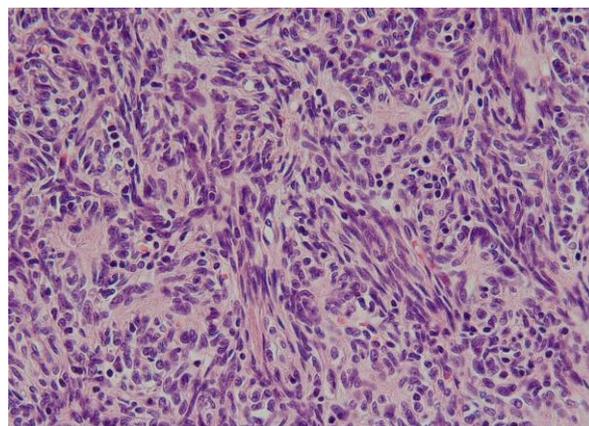
as it was used. Gastric biopsy indicated moderate chronic active gastritis and the presence of *H. pylori* like bacilli. There were nonspecific pathologic changes in duodenum without intraepithelial lymphocytosis. Colonoscopic finding included normal mucosa and pathologic examination identified eosinophilic infiltration in lamina propria with no evidence of IBD and microscopic colitis.

One year later he came back complaining of cough and sputum for a period of 9 months. Broncho-alveolar lavage did not show acid-fast bacilli and PPD test was negative (induration less than 5 mm). His chest CT scan revealed bilateral bronchiectasis and bilateral mosaic pattern (Figure 2).

Laboratory study revealed hypogammaglobulinemia (Table 1) and since then he received treatment with once-a-month IVIG for the diagnosis of good's syndrome. He began to feel loss of vision in his left eye in 2013, one year after the beginning of IVIG therapy.

His left eye best-corrected visual acuity was 5/10 and in his fundus examination a clear media with blurred disk margin and retinal white patch along with retinal vascular sheathing was found (Figure 3).

Slit lamp investigation showed clear cornea, trace cells in the anterior chamber and some cells in the anterior vitreous. Left sided intraocular pressure was 14 mmHg.



**Figure 1. The histopathological findings of thymus in a 57-year-old male with good's syndrome; diffuse growth of polygonal and short spindle cells associated with sinusoidal vasculature. Spindle cells are stained by Pan CK. CD3 highlighted intermingled T-lymphocytes**

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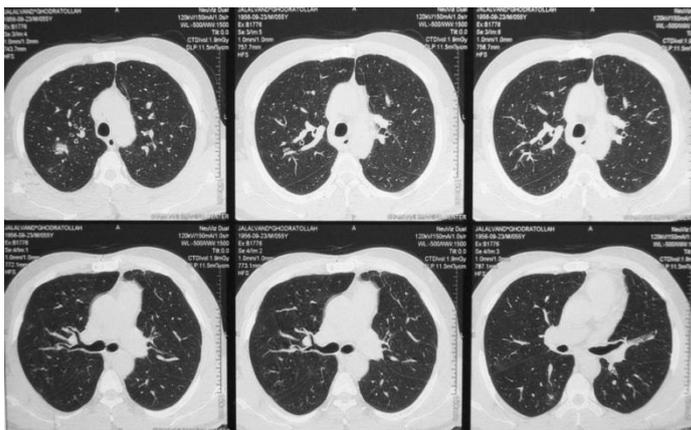


Figure 2. Chest CT-scans showing bronchiectasis and mosaic pattern in a 57-year-old male with good's syndrome

Table 1. Laboratory results of a 57-year-old male with good's syndrome at the first admission

White blood cells	$5 \times 10^3 / \mu\text{L}$
Neutrophils	25%
Eosinophils	6%
Lymphocytes	30%
Monocytes	29%
Hemoglobin	12.8 (13-17gr/dL)
Platelet	$477 \times 10^3 / \mu\text{L}$ (150-410)
Aspartate aminotransferase	Within normal range
Alanine aminotransferase	Within normal range
Total bilirubin	
Immunoglobulin G	310 mg/dL
Immunoglobulin A	30 mg/dL
Immunoglobulin M	20 mg/dL
Immunoglobulin E	6 mg/dL
CD3	93% (35-78)
CD4	31% (22-62)
CD4/CD8	0.5 (1-3)
CD19	1.1% (3-14)
CD16	12.3% (5-19)
CD56	12.4% (3-15)
Tuberculin skin test	Negative (<5 mm induration)
HIV-Ab	Negative
HBS-Ag (ELISA)	Negative
HBS-Ab	56 (Positive) mIU/mL
HCV-Ab	Non- reactive
C3	Within normal range
C4	Within normal range
CH50	Within normal range
ANCA	Negative
CMV-PCR (eye discharge)	Positive

HIV: Human immunodeficiency virus, HBS-Ab: hepatitis B virus antibody, HCV: hepatitis C virus, ANCA: Anti-neutrophil cytoplasmic antibody, CMV: cytomegalovirus



**Figure 3. Fundoscopic examination in a 57-year-old male with good's syndrome**

His serum IgG antibody (380 IU/mL) was positive for cytomegalovirus (CMV). Polymerase chain reaction (PCR) of blood for CMV, herpes simplex virus (HSV) and toxoplasma screening tests were negative. Brain MRI was normal .

Unilateral CMV retinitis was diagnosed according to clinical and laboratory data and treatment with intravitreal gancyclovir for 6 months and then oral valgancyclovir was started. Follow-up examination of the involved retina showed partial response. His left eye best visual acuity after treatment was 10%.

He has been under observation since 2012. Over this time he gradually developed mild macrocytic anemia with Hb 12.4 g/dL (11.5-17 g/dL), MCV 102 fL (80.0-96.0), Vit B12 serum level 80 pg/mL (200-900 pg/mL), serum level of acid folic 8 ng/mL (2-20 ng/mL), ferritin 292 ng/mL (29-336 ng/mL). Folic acid 5mg /day and vitamin B12 1mg/month were prescribed and the patient was observed. His Hb level continued to decrease slowly. In the following year he referred with a feeling of weakness, pallor and powerlessness. His laboratory test showed anemia (Hb 4.7g/dL, MCV: 95.3fL, MCH: 30 pg), ESR 140 mm/h (<15 mm/h), corrected reticulocyte count 0.5, negative direct coombs, normal liver function test except for high alkaline phosphatase (1028 U/L [100-290 U/L]). Diagnostic workup for parvovirus B19, HIV and viral hepatitis were negative. Bone marrow aspiration and biopsy revealed profound erythroid hypoplasia in accordance with pure red cell aplasia (Figure 4). Treatment with prednisolone was recommended. Cyclosporine was started according to the unacceptable

response to the treatment with prednisolone, which was discontinued because of adverse effects.

Nail candidiasis, which was confirmed through smear analysis, was appeared since 2016 and he was treated by topical and systemic anti-fungal (Terbinafin and topical clotrimazol) (Figure 5).

### **Clinical Manifestations of Good's Syndrome**

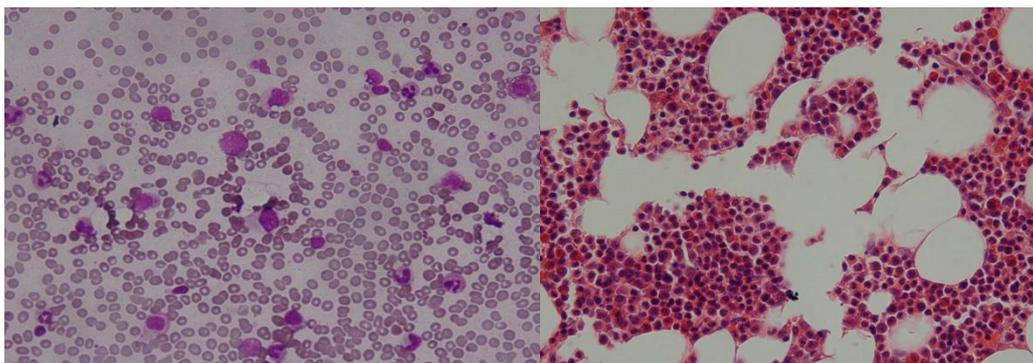
Clinical pictures of thymoma are extremely variable. Sometimes, an accidentally discovered mediastinal mass on chest radiography in an asymptomatic patient is the first presentation. Roughly two third of thymoma patients exhibit local and systemic symptoms, generally represent with cough, dysphagia, dysphonia and chest discomfort.

Numerous autoimmune disorders are accompanied by thymoma as paraneoplastic syndromes. Myasthenia gravis is the most frequent one, happening to about 30-45% of cases that is manifested by dysphagia and respiratory distress due to muscular weakness, followed by hypogammaglobulinemia (good's syndrome) and pure red cell aplasia, with an occurrence rate of 6-11% and 2-5% respectively. However, thymoma could be associated, less commonly with connective tissue disorders such as systemic lupus erythematosus, polymyositis, rheumatoid arthritis, thyroiditis, Sjogren syndrome and ulcerative colitis along with superior vena cava and Horner's syndrome.<sup>11-14</sup>

Moreover, lichen planus and inflammatory bowel disease similar to graft versus host disease have been described as other autoimmune manifestations.<sup>9-15</sup>

Good's syndrome is commonly associated with hematologic manifestations. Anemia is seen in more than half of the patients and comprises pernicious, macrocytic, autoimmune hemolytic and aplastic anemia. Pure red cell aplasia (PRCA) that manifests with a normochromic and normocytic anemia with reduced reticulocyte count and reduced erythroid progenitors is most common autoimmune presentation of good's syndrome. Thymoma is one of the major causes of the secondary PRCA. Myelodysplastic syndromes, neutropenia, lymphopenia, diabetes mellitus, and idiopathic thrombocytopenia are also reported in good's syndrome.<sup>2,7,16,20</sup>

Apart from more frequent occurrence of opportunistic infections in good's syndrome due to concomitant cell mediated immunodeficiency, the clinical features of good's syndrome are comparable to



**Figure 4. Bone marrow biopsy; erythroid hypoplasia was found in bone marrow examination in a 57-year-old male with good's syndrome**



**Figure 5. Nail candidiasis; bilateral big toe nail candidiasis in a 57-year-old male with good's syndrome**

other forms of humoral immunodeficiencies such as x-linked agammaglobulinemia (XLA) and common variable immunodeficiency (CVID). Immunodeficiency might come first (in 19.7% with an average period of 3 months to 15 years) or following (in 42.4% with mean duration of 3 months to 18 years) the documentation of thymoma. Whilst hypogammaglobulinemia is not a common finding in thymoma, once immunodeficiency occurs, it might be rigorous.

Sinopulmonary infections due to encapsulated pathogens are typical manifestations generally appearing between ages of 40 to 50. Patients with good's syndrome are disposed to infection with encapsulated bacteria, opportunistic viruses and fungi. The most common pathogens are *Haemophilus influenzae*, *Pseudomonas* spp., *Klebsiella* spp., *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Moraxella catarrhalis*, and *Serratia* spp. However, *Streptococcus viridans* group B, *Salmonella* sp, *Enterobacter* spp, *Acinetobacter baumannii*, *Mycoplasma pneumoniae*, *Candida albicans* are found in less than 2% of patients. Secondary bronchiectasis is a common complication. As in other hypogammaglobulinemia disorders, gastrointestinal

infections frequently lead to chronic diarrhea and malnutrition. Diarrhea attributable to infection with *Salmonella* spp., *Campylobacter jejuni*, *Clostridium difficile*, *Giardia lamblia* and Cytomegalovirus (CMV) colitis or an inflammatory phenomenon has been found in almost half of good's syndrome patients.<sup>7,12,14</sup> Repeated episodes of giardiasis refractory to treatment with conventional antibiotics and even IVIG has been reported.<sup>21</sup>

Owing to unique cell mediated immunodeficiency has been defined in these patients, opportunistic fungal and viral pathogens more frequently cause infection in good's syndrome. *Candida*, *aspergillus*, *isopora* and *Mycobacterium tuberculosis* have been found as the reasons of mucosal and disseminated infections in patients with good's syndrome.<sup>9</sup> Characteristically, retinitis and colitis assigned to CMV and mucocutaneous involvement by candida infection are common pictures of this entity. Other opportunistic infections including herpes simplex, human herpes virus 8, *Varicella zoster*, and *Pneumocystis jiroveci* have been outlined as well.<sup>10,12,14</sup>

Difficult to treat gastrointestinal ulcers responding to immunoglobulin replacement therapy are reported as

other manifestations of good's syndrome.<sup>22</sup>

Lung involvement comparable with granulomatosis lung disease in CVID has also been reported.<sup>16</sup>

### **Immunologic Features and Pathogenesis**

This condition is demonstrated by loss of B-cells owing to interruption in Pre-B stage, reversed CD4/CD8+ T cell ratio due to CD4+ T cell lymphopenia and T cell malfunction. The resultant combined immunodeficiency might proceed or pursue thymectomy. It has been postulated that autoantibodies or abnormal T cells could play a role in the establishment of immunologic and hematologic defects. The precise mechanism of pathogenesis remains to be defined<sup>2,6,14,23</sup>

Given the principal role of thymus in T cell development, especially the responsibility of thymic epithelial cells in T cell instruction, it would be expected that aberrantly trained T cells are responsible for immune skewing in this condition.<sup>3</sup>

Reduction in the subcategory of mature CD45RA<sup>+</sup> T cell that has been reported in thymoma in contrast to normal thymus indicates the aberrant T cell maturation in the tumor. This might be associated with distribution of auto-reactive T cell subsets to the peripheral circulation promoting autoimmunity.<sup>24</sup> A recently described thymoma with immunodeficiency is associated with naïve  $\gamma\delta$  T cell expansion and low quantity of  $\zeta$   $\zeta$ -chain (CD247) expression in the TCR complex.<sup>25</sup>

Reduced reactions of Th17 and elevated level of autoantibodies against Th17 related cytokines, IL-17 A, IL-17 F and IL-22 have been found in chronic mucocutaneous candidiasis (CMC) associated with thymoma<sup>26</sup>. Autoimmune regulator (AIRE) does not express on thymic epithelial cells in thymoma. This is considered as one of the mechanisms of autoimmunity in good's syndrome for the reason of negative selection impairment.<sup>9</sup>

It has been demonstrated that CD8+ T cells obtained from good's syndrome patients are capable to repress pro-B cell proliferation. B cell absenteeism in peripheral blood and hypogammaglobulinemia ensues as the fundamental immunological outcome.<sup>1</sup>

Diminished serum level of IgG, IgA and IgM, is observed in virtually all patients, meanwhile reduced specific antibody production has been ascertained.

T cell function is thoroughly compromised in good's syndrome. It is illustrated in vivo by skin

unresponsiveness to antigen (anergy) and in vitro by impaired proliferative reaction to mitogens likewise to the substantial devastating impact on cytokine production. It has been verified that CMV infection might happen in good's syndrome even with more abundant T cells opposed to HIV infection. According to the documentation of CMV infection despite normal number and function of CD4+ T cells in good's syndrome, it has been suggested that T cell response to CMV is distinctively abnormal in this entity.<sup>12</sup>

According to the different hematopoietic cells abnormalities leading to maturational arrest of B lymphocytes, T cell cytopenia, diminished myeloid and erythroid lines, it has been postulated that bone marrow is the main origin of the defect<sup>2,7</sup>. There is an assumption that bone marrow stromal cells produce a cytokine similar to interferon that frustrates the differentiation and growth of the B cell precursors in good's syndrome.<sup>12</sup> Nonetheless; plasma cell absenteeism in peripheral and gut associated lymph node indicates the presence of an additional anomaly along with bone marrow.<sup>2,7</sup>

Limited genetic studies have been done in good's syndrome. Mutations in the genes coding the transmembrane activator and CAML interactor (TACI) and B-cell activating factor receptor (BAFF-R) have been reported.<sup>27,28</sup>

### **Management and Prognosis**

Considering the fact that substantial proportion (90-95%) of tumors remains localized, thymectomy, as the first step of treatment, is recommended to remove the tumor mass.<sup>11,29</sup>

The greater extent of tumor resection has been accompanied by a more appropriate outcome. Subsequent radiotherapy and chemotherapy are necessitated for tumors in advanced stages. This approach effectively decreases the local symptoms and has a relatively beneficial impact on some accompanying disorders including myasthenia gravis and pure red cell aplasia but several complications such as hypogammaglobulinemia are generally not completely resolved.<sup>2,7,10,13</sup>

Intravenous immunoglobulin is the principal step in management of good's syndrome. IVIG replacement therapy is necessary to minimize hospital admission and antibiotic requirement through reducing infections.<sup>2,7,10,13</sup>

Cholestyramine has been used for resistant diarrhea.

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Several alternatives such as plasmapheresis, immunosuppressant, splenectomy and leukocyte derived transfer factor are also recommended for management of hematologic complications.<sup>2,7,10</sup>

Considering the risk of opportunistic infections, it is advisable to use prophylaxis for pneumocystis with regard to the level of lymphopenia.<sup>14</sup>

Evaluation of immune system, comprising total number and function of B cells and T cell subclasses, is expected to be considered in thymoma patients who have been shown to be susceptible to infection at the first investigation. Even if the initial assessment is normal, it is valuable to repeat this procedure regularly considering the fact that immunodeficiency occurrence is possible on every occasion.<sup>7,13,14</sup>

Determining the IgG antibodies to cytomegalovirus and toxoplasmosis helps to find the patients who are vulnerable to reactivation of these infections. CMV negative blood products should be considered for the patients with unidentified or negative CMV antibody.<sup>7</sup>

First recommended therapeutic option for pure red cell aplasia is thymectomy that is expected to cause recovery in 25-30% of cases. Anti-thymocyte globulin has been considered as a therapeutic modality but its elevated morbidity attributable to recurrent infections limited its usage. Immunosuppressive agents are required in the majority of patients with pure red cell aplasia related to thymoma. The best response has been reported to cyclosporine A and this drug has been also effective in precluding from relapse. It is noteworthy that the histology of thymoma has a major impact on the response to the immunosuppressive treatment. Other modalities such as splenectomy, plasmapheresis and bone marrow transplantation have been proposed in refractory instances.<sup>18,20</sup>

Thymoma, has a gradual growth and its outcome after thymectomy is good. However, in the presence of paraneoplastic conditions, its prognosis depends on the magnitude of associated disorder.<sup>7,14</sup>

Good's syndrome usually does not cure with thymectomy and its infectious problems determine prognosis. The extent of B cell and T cell dysfunction and the degree of hypogammaglobulinemia are the most important factors contributing in the intensity of infections. When there is an autoimmunity that necessitates immunosuppression, it could intensify the infectious complications.<sup>7,13</sup>

Association of myasthenia gravis with thymoma is considered as a factor for better outcome because of

earlier identification of thymoma and reducing the rate of recurrence.<sup>29</sup>

## DISCUSSION

Good's syndrome is an adult onset combined T cell and B cell immunodeficiency associated with thymoma that presents with recurrent infections and several paraneoplastic syndromes.<sup>2</sup> The immunologic defects may present before or after identification of thymoma. However, thymectomy has not considerable preventive and therapeutic effect on the infectious and non-infectious presentations of good's syndrome.<sup>30</sup> Given the coexistence of T cell dysfunction in addition to the absence of B cell, good's syndrome presents with more complicated and opportunistic infections comparing to CVID and XLA. The common infections are colitis and retinitis attributable to CMV, infections initiated by herpes virus family (HSV, VZV, and HHV8), mucocutaneous candidiasis as well as *pneumocystis jiroveci* pneumonia. Although the enteric bacteria, giardia and CMV are respected as the common causes of chronic and intractable diarrhea in good's syndrome, an inflammatory as well as an idiopathic form of colitis may also have a role.<sup>12</sup>

Good's syndrome is associated with a wide spectrum of paraneoplastic syndromes including myasthenia gravis, pure red cell aplasia, hypogammaglobulinemia, thrombocytopenia, pernicious anemia and numerous autoimmune manifestations. However, coincidence of two or more paraneoplastic syndromes is an extraordinary finding.<sup>30,31</sup>

Herein we reported a case of good's syndrome in a 57-year old man presented with recurrent diarrhea due to *isospora belli*, bronchiectasis, CMV retinitis, pure red cell aplasia and cutaneous candidiasis.

The concomitance of different paraneoplastic syndromes in this patient is appealing. As an opportunistic infection, CMV is known as the reason of septicemia, pneumonia, gastroenteritis and encephalitis in immunocompromised patients.<sup>32</sup> CMV retinitis has been previously reported in patients with good's syndrome<sup>32-35</sup> Assi et al reported CMV retinitis in two women with a history of thymoma and recurrent infections for the first time.<sup>32</sup> Not promptly treated CMV retinitis is a progressive and poor prognostic problem could result in blindness.<sup>37</sup> Considering the reduced number of CD4+ T cells in more than half of

the previously reported good's syndrome patients presenting with CMV retinitis, Downes et al suggested that CMV specific CD4+ T cell reduction due to relative CD4+ T cell deficiency makes patients predisposed to this complication.<sup>35</sup>

PRCA is the primary or secondary interruption of erythropoiesis. Secondary PRCA is seen in hematologic and autoimmune disorders as well as thymoma. It has been reported as the most frequent autoimmunity related to good's syndrome in different case series.<sup>19,37</sup> The real pathomechanism of thymoma associated PRCA is not clear. It has been attributed to auto-reactive T cell groups and autoimmunity. PRCA may appear before or after thymectomy and regardless of immunoglobulin replacement therapy.<sup>7,18</sup> Thymoma accompanied by PRCA reduces the patients' lifespan.<sup>20</sup>

*Candida albicans* is commonly a non-pathogen organism that causes superficial and deep invasive infections in immunocompromised patients. Human T cell especially Th17 subset are responsible for the defense against candida. It has been proposed that thymic tissue damage caused by tumor leads to lower expression of AIRE. This entity impedes tolerance that brings autoimmunity. Autoantibodies against Th17 cytokines in addition to T cell dysfunction has been proposed as the pathogenesis of chronic mucocutaneous candidiasis in good's syndrome.<sup>26</sup>

Even though thymoma is not generally considered as a high grade tumor and is regarded curable after surgical resection, in the case of repeated infection or parathymic disorders, its association with good's syndrome should be taken in account and observed. Physicians should be alert of this condition and measurement of the serum level of immunoglobulin is recommended in any suspicious case.

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