Good’s syndrome with increasing $\gamma\delta$ T-lymphocyte subpopulation: A case report

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Abstract

Introduction. Good’s syndrome is a rare cause of adult-onset immunodeficiency associated with thymoma. Good’s syndrome should be considered in patients older than 40 years with the history of frequent infections. An abnormal immunoglobulin profile needs further investigation and flow cytometry which is crucial for establishing the diagnosis of Good’s syndrome.

Case report. We present a 56-year-old man with Good’s syndrome diagnosed after a two-year history of recurrent infections. Examination of immune status of the patient showed decreased serum levels of all immunoglobulins. Flow cytometry of peripheral blood lymphocyte revealed markedly reduced peripheral B cells, CD4 T-cell lymphopenia, inverted CD4/CD8 T-cell-ratio 0.37 (CD4 – 20.82%, CD8 – 70.7%). Analysis of the subpopulations of T-lymphocytes showed relative increasing $\gamma\delta$ T cell receptor (TCR) T lymphocytes. Computed tomography scan of the chest showed a mediastinal mass compatible with thymoma of the diameter of 40 mm. After initiation of intravenous immunoglobulins the patient was in the good clinical condition and without bacterial complications. As the patient refused the operative treatment we continued to control the mediastinal tumor mass which did not increase during a 3-year follow-up.

Conclusion. The presented patient had a typical immunological finding for Good’s syndrome, but also the increase in $\gamma\delta$ TCR T-lymphocyte subpopulation for which it is difficult to determine whether this is pathogenetic or secondary reactive event.

Key words: acquired immunodeficiency syndrome; thymoma; comorbidity; adult; diagnosis, differential; flow cytometry.

Apstrakt


Ključne reči: imunitet, sindromi stečenog nedostatka; timom; komorbiditet; odrasle osobe; dijagnoza, diferencijalna; citometrija, protočna.
Introduction

Good’s syndrome (GS) is a rare cause of combined B- and T-cell immunodeficiency in adults associated with thymoma. It was first described in 1954 by Good, who reported hypogammaglobulinemia in an adult patient with thymoma. It is a rare type of adult-onset immunodeficiency characterized by hypogammaglobulinemia, lower number or absence of peripheral blood B-cells, and variably, defects in cell-mediated immunity. The patients with Good’s syndrome have a bone marrow defects impairing B-cell maturation and deficiencies in other cell lineages. It was often considered as a subset of common variable immunodeficiency (CVID) with thymoma, whereas nowadays this disorder is classified as a distinct entity by the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency.

We presented the patient with typical immunological findings for Good’s syndrome (hypogammaglobulinemia, few or absent B-cells, CD4+ T-cell lymphopenia and abnormal CD4+/CD8+ T-cell ratio), associated with increasing of γδ T-lymphocyte subpopulation.

Case report

A 56-year-old patient, was hospitalized for the first time in our department in April 2010. His main symptoms were prolonged cough with scanty yellowish sputum during two weeks, diarrhea, with occasionally mucous stools and weight loss. His condition started 2 years before when he had repeated outpatient visits and hospital admissions either from diarrhea or respiratory tract infections (frequent episodes of sinusitis and pneumococcal pneumonia three times). Two months before admission sinus surgery had been done because of frequent sinusitis.

The patient had never smoked, nor consumed alcohol, and his family history was noncontributory.

Physical examination on admission to our hospital revealed a fever of 38.2°C and moist skin. Auscultation of lung sounds showed normal breathing, with inspirium basal crackles in both sides, and there was no hepatosplenomegaly or lymphadenopathy. A complete blood count revealed leukocytosis (11×10⁹/L) with neutrophilia in differential, normal erythrocyte and platelet counts. The patient’s blood chemistry showed elevation of acute phase reactants of inflammation [sedimentation of erythrocytes (SE) 56/1h, C-reactive protein (CRP) 44 mg/L, fibrinogen 5.4g/L)]. Serum levels of all immunoglobulins were decreased (Table 1). Examination of bone marrow aspirate specimen revealed mild hypercellularity without pathological finding. Immunoserological analyses of rheumatic factor, antinuclear antibodies, anion gap metabolic acidosis (AGMA), and cryoglobulins were negative. Antibodies to human immunodeficiency virus were negative. Proteinuria was 0.4 g/24 h. Serum and urine immunofixation did not demonstrate any monoclonal component. Tumor markers were not elevated.

We presented the patient with typical immunological findings for Good’s syndrome (hypogammaglobulinemia, few or absent B-cells, CD4+ T-cell lymphopenia and abnormal CD4+/CD8+ T-cell ratio), associated with increasing of γδ T-lymphocyte subpopulation.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Results I May 2009</th>
<th>Results II Feb 2014</th>
<th>Referent ranges</th>
</tr>
</thead>
<tbody>
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<td>&lt; 0.1</td>
<td>0.7–4.0</td>
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<td>IgM (g/L)</td>
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<td>&lt; 0.01</td>
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<td>IgG (g/L)</td>
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<td>4.2</td>
<td>7.0–16</td>
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<tr>
<td>B-Ly (%)</td>
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<td>0</td>
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<tr>
<td>T-Ly (%)</td>
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<td>89</td>
<td>65–84</td>
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<tr>
<td>T-Ly (cell/µl)</td>
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<td>1602</td>
<td>1,084–2,822</td>
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<tr>
<td>CD4+ T-Ly (%)</td>
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<td>20</td>
<td>32–57</td>
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<tr>
<td>CD4+ T-Ly (cell/µl)</td>
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<tr>
<td>CD8+ T-Ly (%)</td>
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<td>CD8+ T-Ly (cell/µl)</td>
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<tr>
<td>γδ T-Ly (% of T-Ly)</td>
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<tr>
<td>NK cells (CD3+CD16+CD56+)</td>
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<td>NK cells (CD3+CD16+CD56+)/µL</td>
<td>271</td>
<td>378</td>
<td>208–1,097</td>
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</table>

Ig – immunoglobulin; Ly – lymphocytes; NK cells – natural killer cells.
T-lymphocyte subpopulation (11% of T-cells).

After a 2-year history of recurrent infections. The diagnosis of Good’s syndrome was established when he was 20% of cases, thymoma is diagnosed 3 months to 15 years after diagnosis of hypogammaglobulinemia (42%), infection, or diarrhea. In 38% cases, in other cases diagnosis tymoma preceded the diagnosis of hypogammaglobulinemia (42%), infection, or diarrhea. In 20% of cases, thymoma is diagnosed 3 months to 15 years after other clinical manifestations. In the presented patient thymoma and hypogammaglobulinemia were diagnosed simultaneously, but after a 2-year period of frequent infection.

The main clinical characteristics of Good’s syndrome are increased susceptibility to bacterial infections, opportunistic viral and fungal infections. Most patients experienced recurrent sinopulmonary infections secondary to encapsulated organisms (Haemophilus influenzae, Streptococcus pneumoniae), skin infections, bacterial diarrhea (Giardia lamblia, Salmonella spp, Campylobacter jejuni) and urinary tract infections. The most common virus infection is caused by cytomegalovirus. Infections caused by herpes simplex virus, human herpes virus type 8 and varicella-zoster virus are also frequent. Although systemic fungal infections are not characteristic for Good’s syndrome, mucocutaneous candidiasis occur.

Discussion

Good’s syndrome, defined as thymoma associated with immunodeficiency, is a rare cause of combined B- and T-cell immunodeficiency in adults, represented with a similar frequency in male and female patients. It can occur in children, although this is extremely rare. Its exact prevalence is unknown but it only represents 1% to 2% of patients, which are treated by intravenous immunoglobulin (IVIG) therapy for a primary deficiency of immunoglobulins. Patients with Good’s syndrome usually present in the 4th or 5th decade of life. According the literature data, the mean age of initial symptoms was 56 years (range, 29–75). Similarly, in the presented patient the diagnosis of Good’s syndrome was established when he was 56 after a 2-year history of recurrent infections.

The pathogenesis of Good’s syndrome is unknown, but there are two hypotheses. In vitro studies showed defects in B-cell precursor growth and differentiation and T-lymphocyte proliferation as well as interleukin-2 production. It has been demonstrated that T-lymphocytes from patients with thymomas can inhibit immunoglobulin production in healthy controls. Loss of B-cell function is probably due to autoimmune destruction by T-cells or autoantibodies. It is supported by the frequent association of Good’s syndrome and various autoimmune diseases. They include pure red cell aplasia, myasthenia gravis, oral lichen planus, aplastic anemia, macrocytic anemia, leucopenia, thrombocytopathy, monoclonal gammopathy and autoimmune hemolytic anemia.

The principal immunological findings in Good’s syndrome are hypogammaglobulinemia, few or absent peripheral blood B-cells, an abnormal CD4+/CD8- T-cell ratio, CD4+ T-cell lymphopenia, and impaired T-cell mitogenic responses. Almost all patients have reduced serum IgG, IgA and IgM. Flow cytometric immunophenotyping of peripheral blood lymphocytes of our patient showed all of changes consistent with Good’s syndrome. Besides, relative increasing of γδ T-lymphocyte subset was noticed, which was persistent finding after a 5-year follow-up. Lymphocyte bearing the γδ TCR comprise a small proportion (5%) of the total peripheral blood lymphocytes. An increased proportion of circulating γδ T-cells has been found in infections, T-cell leukemia as well as in patients with some primary immunodeficiencies, such as CVID, Wiskott-Aldrich syndrome, ataxia telangiectasia, with or without infections at the time of evaluation. It is not known whether increasing of γδ T-lymphocytes is a primary event involved in the pathogenesis of the disease or a reactive event emerged as the consequence of the disease or chronic antigenic stimulation induced by bacterial or viral antigens. It has been hypothesized that γδ T-lymphocytosis may arise from dysregulation of γδ TCR gene expression in association with defects in αβ TCR gene expression. It was supported by the finding of markedly reduced CD4+/CD8+ T-cell index as observed in the presented patient.

The initial clinical presentation is either a mass-lesion thymoma or a recurrent infection. Thymoma occurs in 10% of patients with adult-onset hypogammaglobulinemia, whereas 6–11% of thymoma patients have hypogammaglobulinemia. Thymoma associated with infections appear almost simultaneously in 38% cases, in other cases diagnosis tymoma preceded the diagnosis of hypogammaglobulinemia (42%), infection, or diarrhea. In 20% of cases, thymoma is diagnosed 3 months to 15 years after other clinical manifestations. In the presented patient thymoma and hypogammaglobulinemia were diagnosed simultaneously, but after a 2-year period of frequent infection.

Bearing in mind the above findings, diagnosis of Good’s syndrome was established. Thus, the patient was treated with intravenous polyclonal immunoglobulins in the four-week intervals. After initiation of intravenous immunoglobulins, the patient was in good clinical condition and without bacterial complications, but with recurrent episode of herpes zoster infection. The mediastinal tumor mass was regularly monitored by CT scan and did not increase during a 4-year follow-up. Control flow cytometric immunophenotyping of peripheral blood, after a 5-year follow-up, confirmed the persistence of absolute B-cell lymphopenia, CD4+ T-cell lymphopenia (360 cells/μL), as well as inverted CD4+/CD8 T-cell ratio (0.47). Moreover, a relative increase of γδ T-lymphocyte subpopulation was detected (30% of T-cells).

Discussion

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in 24% of cases. The presented patient had a typical history of recurrent sinopulmonary and skin infection and diarrhea that was the reason for immunological examination.

The prognosis of Good’s syndrome is worse than X-linked agammaglobulinemia (XLA) and CVID and mortality of approximately 45% has been reported in a systematic review of 152 patients with this syndrome. Thymoma itself is not believed to contribute towards excess mortality in this condition. The predominant causes of death are infections associated with immunodeficiency.

Treatment of antibody deficiency in GS requires supplementary intravenous immunoglobulin replacement to maintain adequate levels of immunoglobulin. Their use improves infection control, reduce hospitalization and decrease the use of antibiotics. The treatment of thymoma is surgical removal or debulking of the tumor and the most important indicator of a standard for determination of immunological defects. Increasing awareness about the clinical and immunological profile of this syndrome may increase its early recognition and prevent mortality. Further studies are needed to elucidate the pathogenesis and significance of γδ T-lymphocyte subpopulation in this clinical entity.

Conflict of interests

The authors declare that they have no conflict of interests.

References


