CLINICAL REPORT

Immunological disturbances in Good's syndrome

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Abstract

Background: Immunodeficiency with a thymoma (Good's syndrome) is a rare condition occurring in patients with adult-onset hypogammaglobulinaemia.

Clinical report: We describe the case of a 38-yr-old woman with an upper mediastinal mass and inflammatory infiltrations in the lungs. After thymectomy, the patient's condition did not improve. The HRCT scan showed bronchiectasies with parenchymal opacities. As pulmonary infection persisted despite wide spectrum antibiotic therapy, additional tests were performed to diagnose an immunodeficiency. Serum immunoglobulin levels were very low. T cell response to mitogens was normal, but to *Staphylococcus aureus* Cowan I was impaired. Immunophenotyping of peripheral blood and bone marrow aspirate showed a very low number of B-cell at all the stages of development (CD10+CD19+, CD5+CD20). In peripheral blood 2.5% of CD19+ lymphocytes were found. On the basis of clinical history and immunological analysis, Good's syndrome was recognized. Treatment with intravenous gammaglobulin and antibiotics improved the patient's performance.

Conclusion: Measurement of serum immunoglobulin concentration is recommended for all patients suspected of thymoma.

Good's syndrome, a rare coincidence of thymoma and immunodeficiency, was first described over 50 years ago.¹ The syndrome occurs in 7 to 13% of patients with adult-onset hypogammaglobulinaemia, and in 6-11% of patients with thymoma.¹ The principal immunological findings in Good's syndrome are hypogam-

maglobulinaemia, few or absent B cells, an abnormal CD4+/CD8+ T cell ratio, CD4+ T cell lymphopenia and impaired T cell mitogenic response.¹ The clinical characteristics of Good's syndrome include increased susceptibility to bacterial infection with encapsulated organisms, as well as opportunistic viral and fungal infections.² The cause and pathogenesis of the disorder are unknown, although some evidence points to a basic defect in the bone marrow (pre-B cell arrest, impaired maturation of erythroid and myeloid precursors in some patients).¹

There are very few publications describing bone marrow abnormalities in Good's syndrome patients. We describe the case of a woman with Good's syndrome in the light of immunological disturbances.

Case report

A 38-year-old, non-smoking woman, school-teacher, was admitted to the Regional Pulmonary Hospital in June, 2006 because of persistent cough, fever and gradual loss of weight during the last 6 months. Previously, she was healthy and she had no history of increased susceptibility to infection. The HIV test was negative. On admission, an upper mediastinal mass and inflammatory infiltrations in the lungs were found. The patient was sent to the Thoracic Surgery Department at the Institute of Tuberculosis and Lung

FIGURE 1. Lack of B-cells and B-cell precursors in bone marrow from Good syndrome patient (A – CD3/CD22 phenotype; B – CD10/CD19 phenotype; C – CD5/CD20 phenotype).

FIGURE 2. Thymoma. Hematoxylin/eosin staining (x 200).

Diseases (ITLD), Warsaw for further treatment. In September, 2006 thymectomy with lymph node dissection was performed. Histological examination showed Masaoka stage II type AB (mixed) thymoma (fig. 1 and fig. 2). A lung biopsy specimen (left lower lobe) demonstrated fragments of alveolar parenchyma with inflammation, intra-alveolar purulence consistent with organizing pneumonia. Neoplastic cells were not found. After surgery, a transient leukopenia (WBC count $2,8 \times 10^3$ cells/mm³) was observed.

The patient's condition did not improve. She continued to complain of cough and fever so antibiotic therapy was introduced. Control CT scan was performed in March 2007 showed bronchiectasies. Thymoma recurrence was suspected and the patient was readmitted to ITLD. At admission the patient presented with fever and cough. Physical examination showed oral herpetic ulceration, rhinitis and fine crackles overall lung fields. Chest X-ray revealed nodular opacities in both lungs. HRCT showed considerable progression of bronchiectasies, compared with the preoperative scan, with parenchymal opacities. Thymoma regrowth was excluded and sinusitis was diagnosed. Blood gas analysis revealed PaO₂ 5.8

kPa and oxygen saturation of 92%. Pulmonary function test demonstrated restrictive and constrictive ventilatory defect. Laboratory tests revealed the following abnormalities: C reactive protein 11.5 mg/l (normal <5 mg/l); total serum protein level 6.1 g/L, hemoglobin 13.3g/dL; WBC count 3.83×10^3 cells/mm³ (61% polymorphonuclear leukocytes, 5% bands, 25% lymphocytes, 3% atypical lymphocytes and 6% monocytes). Toxic granules were found in the granulocytes. The erythrocyte count was 4.41×10^6 cells/mm³ with anisocytosis and ovalocytosis. Platelet count was 262×10^3 /mm³, with platelet anisocytosis.

Pulmonary infection persisted despite wide spectrum antibiotic therapy and additional tests were performed to diagnose immunodeficiency. Chemiluminescence of polymorphonuclear cells was normal. Serum immunoglobulin levels were very low: IgG 0.037 g/L (normal range 7-16 g/L); IgM 0.003 g/L (normal range 0.4-2.3 g/L); and IgA 0.001 g/L (normal range 0.7-4 g/L). Peripheral blood T cell response to mitogens, such as phytohaemagglutinin (PHA), was normal, but the response to *Staphylococcus aureus* Cowan I (SAC) was impaired (276 cpm, normal range 775-5692 cpm). Bone marrow smear contained 19% lymphocytes (including 1% activated lymphocytes); 65.5% neutrophil and neutrophil precursors in all stages of development; 12.5% normoblastic erythropoietic cells; 2% monocytes and 1% megakaryocytes. Myeloid:erythroid ratio was increased (5:1). No plasma cells were found. Immunophenotyping of peripheral blood and bone marrow aspirate was performed by flow cytometry using monoclonal antibodies against human leukocyte antigens (Table 1). Peripheral blood flow cytometry showed very low number of cells with B-cell markers (CD19+, CD20+ and CD22+), reduced number of CD4+ T cell and CD56+ cells and decreased CD4:CD8 ratio (1.6) (Table 1).

The percentage of B-lymphocytes and its precursors in bone marrow was low (< 1% lymphocytes), 14.8% of cells expressed HLA-DR antigen (1.9% monocytes, 3.7% activated CD4 cells and 6.3% activated CD8 cells and < 1% B cells). In bone marrow a

FIGURE 3. Thymoma. Immunohistochemical cytokeratin staining (CKAE1/AE3). (x 400).

very low number of B-cells in all the stages of development (CD10+CD19+, CD5+CD20) was observed (fig.3). In peripheral blood 2.5% of lymphocytes with B-cell marker (CD19) was found – probably deriving from peripheral lymph nodes rather than from bone marrow. The number of cells with T cell markers was normal in both bone marrow and peripheral blood. The percentage of naïve CD4 and CD8 cells was reduced but the percentage of memory T cells was normal (Table1). Tuberculin and aspergillin skin tests were negative. Sputum smear revealed no pathogens, apart from *Candida albicans*, and microbiological examination of sputum and blood was negative. Polymerase chain reaction (PCR) of blood sample for cytomegalovirus (CMV), herpes virus -1 (HSV1), human herpes virus – 8 (HHV8) and varicella zoster virus (VZV) was negative. Furthermore, the patient developed clinical symptoms and signs of sinusitis. On the basis of clinical history and immunological analysis Good's syndrome was recognized. Treatment with intravenous gammaglobulin (IVIG) substitution and antibiotics resulted in improvement of the patient's performance (normalization of body temperature and moderation of cough).

TABLE 1. Flow cytometry immunophenotyping of bone marrow and peripheral blood cells from patient with Good syndrome.

Bone marrow cell population positive for	% of cells in gate low FS vs. SS		Peripheral blood cell markers	% of cells in gate low FS vs. SS	
	patient	healthy control range		patient	healthy control range
CD45 ^{dim}	3.5	1-5	CD45 ^{bright} CD14 ⁻	31.4	21- 35
CD45 ^{bright}	10.5	10-20	CD45 ^{middle} CD14 ⁺	7.6	3-12
CD34 HLA DR CD14	1.9	3-7	CD45 ^{dim} CD14 ⁻	58.6	62-81
CD45 ^{bright} CD65	23.4				
CD45 ^{bright} CD2	61.4	59.2-80.6	CD45 ^{bright} CD2	97.7	60-86
CD45 ^{bright} CD3	47.2	48.5-70.2	CD45 ^{bright} CD3	81.2	58-82
CD45 ^{bright} CD3CD4	29.7	22.3-34.3	CD45 ^{bright} CD3CD4	33.7	34-44
CD45 ^{bright} CD3CD8	18.5	16.3-21.4	CD45 ^{bright} CD3CD8	28.2	20-32
CD45 ^{bright} CD3CD8CD4	3.7	0-4	CD45 ^{bright} CD3CD8CD4	1.33	0-2
CD45 ^{bright} CD3CD4 HLA DR	5.3	7-11	CD45 ^{bright} CD3CD4 HLA DR	3.2	0-5
CD45 ^{bright} CD3CD8 HLA DR	6.3	16-20	CD45 ^{bright} CD3CD8 HLA DR	3.9	0-4
CD4CD45RA	0.43	15-31	CD4CD45RA	13.1	15-31
CD4CD45RO	8.5	8-26	CD4CD45RO	19.8	8-26
CD8CD45RA	0.73	16-32	CD8CD45RA	12.0	16-32
CD8CD45RO	2.75	2-15	CD8CD45RO		
CD45 ^{bright} CD5	54.7	59.9-79.8	CD45 ^{bright} CD5	83.8	50-79
CD45^{bright} CD19	0.47	16.2-28.5	CD45^{bright} CD19	0.74	8-20
CD45^{bright} CD20	0.48	11.2-18.3	CD45^{bright} CD20	0.9	4-10
CD45^{bright} CD22	0.8	17.3-30.2	CD45^{bright} CD22	2.6	8-20
CD45^{bright} HLA DR	14.8	9.7-16.3	CD45^{bright} HLA DR	31.5	12-16
CD2CD56CD16			CD2CD56CD16	10.4	5.1-12.2

Discussion

Good's syndrome presents as a rare form of combined B and T cell immunodeficiency in adults with thymoma. Although there are no formal diagnostic criteria - it is classified as a distinct entity by the expert committee of the World Health Organization/International Union of Immunological Societies on primary immunodeficiencies.³ Good's syndrome is noted in around 7% of adults with primary antibody deficiency.³ In patients with thymoma the incidence of hypogammaglobulinaemia is 6–11%.⁴ Good's syndrome usually manifests itself in the 4th or 5th decade on the life, without preference to either sex. The immunodeficiency may precede or occur after the diagnosis of thymoma.⁴ In our patient, immunodeficiency was recognized 7 months after thymectomy although

the first symptoms of infections appeared 6 months before diagnosis of thymoma.

The principal immunological findings in Good's syndrome are hypogammaglobulinaemia, few or absent B cells, abnormal CD4⁺:CD8⁺ T cell ratio, CD4 T cell lymphopenias, and impaired T cell mitogenic response. Almost all patients have reduced IgG, IgA and IgM. If serum IgG is > 3 g/L, measurement of specific antibodies to a panel of protein and carbohydrate antigens should be undertaken. If IgG concentration is <3 g/L, as in present case, serology is unreliable and the detection of viral or protozoan antigens using the PCR should be undertaken. A reduced mature B cell count or even the absence of B cells, was noted in 87% of cases and the absence of pre-B cells has been reported in bone marrow samples from

patients with Good's syndrome (1). In described case a very low number of cells bearing B cell markers was observed. Both mature B cells and B-cell precursors in bone marrow were almost absent (less than 1%). In peripheral blood the number of CD19 positives cells was around 2.5% of cells. Some of those cells may be of lymphnodes origin. CD4+ T cell lymphopenia and abnormal CD4+:CD8+ T cell ratio is seen in large numbers of patients. T cell defects can be manifested by cutaneous anergy to 2 or more test antigen, for example to tuberculin (absent delayed hypersensitivity) and impaired response to mitogens (1,3). Our patient demonstrated all immunological abnormalities, including impaired mitogenic response to SAC. Although T-cell proliferative response to PHA was normal. The number of naïve thymus derived T cells (both CD4 and CD8) was decreased as well as CD4:CD8 ratio. In described case we have observed pronounced B cell defect together with discrete disturbances in the population of T cells. Clinical characteristics of Good's syndrome include increased susceptibility to bacterial and opportunistic infection. The most common presentation in our patient was recurrent sinopulmonary infection. Infection is secondary to encapsulated organisms (such as *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Staphylococcus aureus*).³ Patients may also experience bacterial urinary tract and skin infections and, sometimes, arthritis. Opportunistic infections are common and their occurrence is associated with disorders of cell-mediated immunity. Viral infection was noted in 40% of patients with Good's syndrome. The common pathogen was CMV, although it can be difficult to distinguish latent infection from active disease. CMV probably did not influence mortality and morbidity.^{1,5} Opportunistic infection caused by HSV-1, HHV-8, VZV, and *Pneumocystis jiroveci* (PJ) pneumonia have also been described.⁵ Systemic fungal infection is not a common feature of Good's syndrome. However, mucocutaneous candidiasis has been diagnosed in 24% of cases.¹

Diarrhea has been reported in almost 50% of patients with Good's syndrome. Enteric bacteria (*Campylobacter jejuni*, *Salmonella*), giardia, and CMV, occasionally, have been isolated from patients' stool although, in most cases, no definite pathogen was identified.^{1,2}

In the present case, pulmonary infection was probably due to typical encapsulated organisms, responsive to standard antibiotic therapy. In addition, HSV-1 mucocutaneous infection was observed. PCR tests for other viruses and *Pneumocystis jiroveci*, were negative and diarrhea was not observed.

Radiological findings in the thymoma - hypogammaglobulinaemia syndrome usually show mediastinal masses and/or pulmonary infiltrates secondary to infection. CT allows for the characterization of tumour and describes possible invasion into surrounding structures.⁶ High-resolution CT is helpful for the detection of pulmonary abnormalities, especially fast progressive bronchiectasies which are very frequent in Good's syndrome patients.⁷ Such a picture was present in our patient.

Treatment of Good's syndrome involves resection of the thymoma, intravenous immunoglobulin (IVIG) replacement to maintain adequate IgG values and antibiotic treatment, if necessary. Therapy with IVIG can reduce the risk of infection, excess antibiotic administration, hospitalization, and the development of pulmonary damage.⁸ In contrast to other paraneoplastic disorders associated with thymoma (e.g. pure red cell aplasia, myasthenia gravis), hypogammaglobulinaemia is not influenced by thymectomy^{1,8,9} as was demonstrated in our patient.

Mortality is considerably higher in patients with Good's syndrome than in patients with X-linked agammaglobulinaemia (XLA) or common-variable immunodeficiency (CVID).^{1,3} Seventy per cent of patients with Good's syndrome survived five years after diagnosis compared with almost 100% of patients with XLA or CVID. After 10 yr, only 33% were alive compared with 95% of patients with XLA or CVID.¹⁰ The clinical course of Good's syndrome

may be more severe in the substantial minority of patients who require immunosuppressive treatment for associated autoimmune conditions. The principal causes of death in Good's syndrome patients are infection, autoimmune disease, or haematological complications.

Conclusion

Serum immunoglobulin level measurement is recommended for all patients suspected of thymoma. If results are in the normal range and clinical suspicion of Good's syndrome persists, the tests should be repeated periodically, given the well-described interval that can occur between the infectious complications of the immunodeficiency and the diagnosis of thymoma (or vice versa). Good's syndrome should be considered in patients with thymoma or unexplained hypogammaglobulinaemia, especially in patients with a history of recurring infection.

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