

## REVIEW

# What is Good's syndrome? Immunological abnormalities in patients with thymoma

P Kelleher, S A Misbah

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Good's syndrome (thymoma with immunodeficiency) is a rare cause of combined B and T cell immunodeficiency in adults. The clinical characteristics of Good's syndrome are increased susceptibility to bacterial infections with encapsulated organisms and opportunistic viral and fungal infections. The most consistent immunological abnormalities are hypogammaglobulinaemia and reduced or absent B cells. This disorder should be treated by resection of the thymoma and immunoglobulin replacement to maintain adequate trough IgG values.

patients. The immunodeficiency may precede<sup>6</sup> or occur after the diagnosis of a thymoma.<sup>6–9</sup>

"The cause and pathogenesis of this disorder are unknown, although there is some evidence that the basic defect may be in the bone marrow"

The initial clinical features of Good's syndrome are varied.<sup>10</sup> The initial diagnosis may be prompted by the finding of an asymptomatic anterior mediastinal mass on chest x ray. Patients may complain of symptoms secondary to the thymoma itself such as cough, chest pain, dysphagia, dyspnoea, and hoarseness. The superior vena cava syndrome, Horner's syndrome, and masses in the neck have all been reported as initial manifestations of this disorder. Thymoma may also be discovered during the routine investigation of myasthenia gravis in patients over 40. Finally, patients may present with infection as a result of the defects in humoral and cellular immunity associated with a thymoma.

The most common cause of infection in this patient population is recurrent sinopulmonary infection secondary to encapsulated organisms.<sup>6</sup> The clinical picture is similar to that seen in patients with X linked agammaglobulinaemia (XLA) and common variable immune deficiency (CVID). Patients also experience bacterial urinary tract and skin infections,<sup>6</sup> and one case of mycoplasma arthritis has been reported.<sup>11</sup> In contrast to XLA and CVID, opportunistic infections associated with disorders of cell mediated immunity commonly occur in Good's syndrome. In particular, cytomegalovirus (CMV) colitis and retinitis and mucocutaneous candida infection are prominent features of this condition.<sup>6</sup> Opportunistic infection caused by herpes simplex,<sup>12</sup> human herpesvirus 8,<sup>13</sup> varicella zoster,<sup>8</sup> and *Pneumocystis carinii* pneumonia<sup>4</sup> have also been described. Isolated defects in cell mediated immunity giving rise to opportunistic viral and fungal infections have also been described in patients with thymomas.<sup>14–16</sup>

Diarrhoea has been reported in almost 50% of patients with Good's syndrome.<sup>6</sup> Enteric bacteria, giardia, and CMV have been isolated from

The association between the presence of a thymoma and immunodeficiency was first recognised in 1954 by Dr Robert Good, who described a case of thymoma and hypogammaglobulinaemia in an adult.<sup>1</sup> Although there are no formal diagnostic criteria for this disorder it is classified as a distinct entity by the expert committee of the World Health Organisation/International Union of Immunological Societies on primary immunodeficiencies.<sup>2</sup> Good's syndrome was noted in 7% of adults with primary antibody deficiency attending a chest clinic,<sup>3</sup> although this figure is probably influenced by referral bias, and the incidence of this condition in patients with primary antibody deficiency who are on immunoglobulin replacement treatment is more likely to be 1–2%. In patients with thymoma the incidence of hypogammaglobulinaemia is 6–11%.<sup>4,5</sup> The cause and pathogenesis of this disorder are unknown, although there is some evidence that the basic defect may be in the bone marrow (pre-B cell arrest, impaired maturation of erythroid and myeloid precursors in some patients).

## CLINICAL FEATURES

Patients with Good's syndrome usually present in the 4th or 5th decade of life. In a literature review of the infectious complications of this disorder the mean age of initial symptoms was 56 years (range, 29–75) and the mean age for the recognition of thymoma and hypogammaglobulinaemia was 62 years (range, 41–79).<sup>6</sup> The interval between the start of initial symptoms and the diagnosis of Good's syndrome is similar to that noted for patients with primary antibody deficiencies in the UK.<sup>7</sup> Good's syndrome can occur in children, although this is extremely rare,<sup>8</sup> and it occurs with similar frequency in male and female

See end of article for authors' affiliations

Dr P Kelleher, Department of Immunology, St Mary's Hospital, Praed Street, London W2 1NY, UK; peter.kelleher@st-marys.nhs.uk

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**Abbreviations:** CMV, cytomegalovirus; cpm, counts per minute; CT, computed tomography; CVID, common variable immune deficiency; HIV, human immunodeficiency virus; IL, interleukin; PHA, phytohaemagglutinin; XLA, X linked agammaglobulinaemia

patients with diarrhoea, although in most cases no definite pathogens were identified. It is thought that an inflammatory colitis similar to that described in CVID may be responsible; however, there are no systematic studies evaluating the nature of idiopathic diarrhoea in this disorder. Patients with Good's syndrome often have autoimmune conditions (myasthenia gravis, pure red cell aplasia, pernicious anaemia, diabetes mellitus, and idiopathic thrombocytopenia).<sup>2</sup> In one of the earliest reviews of this disorder pure red cell aplasia was noted in 35% of cases.<sup>17</sup>

## LABORATORY FEATURES

### Haematology

Good's syndrome is frequently associated with haematological disorders. Anaemia is present in over 50% of patients.<sup>18</sup> Pure cell aplasia,<sup>19</sup> aplastic anaemia,<sup>20</sup> haemolytic anaemia,<sup>21</sup> and pernicious anaemia<sup>22</sup> have all been described. Approximately 55% of patients have a low white blood cell count and 20% have thrombocytopenia.<sup>18</sup> Neutropenia occurs in 18% of patients with Good's syndrome.<sup>6</sup> The absence of eosinophils in blood and bone marrow has been noted in individual case reports.<sup>23</sup> Monoclonal gammopathies (benign and malignant)<sup>24,25</sup> and T cell tumours<sup>26</sup> have been described in Good's syndrome.

### Microbiology

Tarr and colleagues have reviewed the pathogens reported in 51 patients with Good's syndrome (table 1).<sup>6</sup> The most common pathogens isolated in this condition were encapsulated bacterial organisms. *Haemophilus influenzae* was grown in 24% of cases and *Streptococcus pneumoniae* was isolated in another 8%. *Pseudomonas* spp, *Klebsiella* spp, and other Gram negative organisms were isolated from patients with bronchiectasis. *Giardia lamblia* and enteric bacterial pathogens (*Salmonella* spp, *Campylobacter jejuni*) were found in those with chronic diarrhoea. Systemic fungal infections are not a feature of Good's syndrome; however, mucocutaneous candidiasis was diagnosed in 24% of cases.

Viral infections were noted in 40% of patients. The most common pathogen was CMV (24%), although it can be difficult to distinguish latent infection from active disease and CMV probably did not influence mortality and morbidity in some individuals. A list of other viruses isolated in Good's syndrome can be found in table 1. In contrast to human immunodeficiency syndrome, there were only two cases of *Mycobacterium tuberculosis*, and no cases of *Toxoplasma gondii* and *Cryptococcus neoformans* infection have been described in Good's syndrome. Whether the prevalence of these organisms in the population reported to date is different to that documented in other patients with disorders of cell mediated immunity is not known.

**Table 1** Microorganisms associated with infection in patients with Good's syndrome

Bacteria	Viruses
<i>Haemophilus influenzae</i>	Cytomegalovirus
<i>Streptococcus pneumoniae</i>	Herpes simplex
<i>Staphylococcus aureus</i>	Varicella zoster
<i>Salmonella</i> spp	Human herpesvirus 8
<i>Campylobacter jejuni</i>	
Fungi	Protozoa
<i>Candida albicans</i>	<i>Giardia lamblia</i>
<i>Pneumocystis carinii</i>	

## Immunology

The principal immunological findings in Good's syndrome are hypogammaglobulinaemia, few or absent B cells, an abnormal CD4+ : CD8+ T cell ratio, CD4 T cell lymphopenia, and impaired T cell mitogenic responses (table 2). Almost all patients have reduced serum IgG, IgA, and IgM, although there are reports of individuals with normal IgA values<sup>6</sup> and raised IgM concentrations.<sup>23</sup> There are very limited data on the prevalence of reduced specific antibody values. Early studies documented reduced blood group isohaemagglutinins and specific antibody values<sup>27,28</sup> with impaired test immunisation responses; however, the concentrations of IgG were such that these findings were not unexpected.

"In contrast to X linked agammaglobulinaemia and common variable immune deficiency, opportunistic infections associated with disorders of cell mediated immunity commonly occur in Good's syndrome"

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.<sup>29-31</sup> The data on abnormalities in T cell counts and function are limited, although CD4+ T cell lymphopenia and an abnormal CD4+ : CD8+ T cell ratio are seen in large numbers of patients. Studies of cell mediated immunity in Good's syndrome emphasised that T cell defects, as manifested by cutaneous anergy to two or more test antigens,<sup>32,33</sup> or delayed rejection of skin allografts,<sup>28,34</sup> were common features of this condition. Overall, 45% of patients have impaired T cell responses to mitogens such as phytohaemagglutinin (PHA). Further characterisation of T cell proliferative responses to PHA has revealed significant impairment in T cell cytokine production.<sup>6,9</sup> Analysis of cellular immunity in Good's syndrome has revealed that opportunistic infections such as CMV can occur in the presence of significantly greater T cell numbers than is seen in human immunodeficiency virus (HIV) infection. CMV has been documented in the presence of normal CD4+ T cell counts and normal T cell proliferative responses to PHA stimulation.<sup>6,35</sup> In addition, one case report of a patient with CMV encephalitis showed that the patient had a reduction in specific T cell proliferative responses to CMV in the presence of a normal T cell proliferation to PHA.<sup>36</sup>

The immunological findings in Good's syndrome have several limitations. Data on immune function are derived from case reports or small series. A comprehensive immunological evaluation is found in 25% of reported cases (table 2). There are no comparative data for age matched or appropriate disease controls (patients with CVID or Good's syndrome without infectious complications). In general, the analysis of lymphocyte subsets is documented either on a single occasion or when the patient had a systemic infectious illness, which

**Table 2** Immunological findings reported in 75 cases of Good's syndrome

	Normal	Reduced	Number of patients
Serum IgG, IgA, and IgM*	0	75	75
B cell number/%	5	33	38
CD4 positivity T cell number/%	11	9	20
CD4+:CD8+ T cell ratio	8	22	30
Absent delayed hypersensitivity	2	12	14
PHA T cell stimulation	12	8	20

\*One patient had a normal IgA concentration and two had normal IgM values. The total number of cases of thymoma and antibody deficiency was 75. No patients with human immunodeficiency virus infection were included in this review. References for this table are available from the authors on request. PHA, phytohaemagglutinin.

can influence the numbers and proportions of T cells.<sup>37</sup> Several case reports document CD4+ and CD8+ T cell percentages only, or abnormal CD4+ : CD8+ T cell ratios, which limits comparison with those where CD4+ and CD8+ T cell numbers are documented. Finally, several different technologies have been used to study lymphocyte subsets, although since the mid 1980s flow cytometry has superseded all other methods.

### IMMUNOLOGICAL INVESTIGATIONS IN GOOD'S SYNDROME

Good's syndrome should be suspected in patients aged more than 40 years with antibody deficiency. Opportunistic infection, absent, or reduced numbers of mature B cells should be clinical cues to the presence of this disorder in patients with presumed CVID attending an immunology clinic. Serum immunoglobulins should be considered as part of the routine diagnostic investigation for a patient who presents with an anterior mediastinal mass. A reduction in serum immunoglobulins, a history of recurrent sinopulmonary infections, or opportunistic infections, such as CMV or mucocutaneous candidiasis, should be clinical cues to the presence of Good's syndrome in patients with thymomas who attend chest or oncology clinics.

All patients with thymoma should have immunoglobulin values and B and T cell subsets measured. If these are normal, repeat immunoglobulin measurements should be performed every second year because cases of progressive immunodeficiency have been described.<sup>34</sup> An abnormal immunoglobulin profile needs further immunological investigation. Flow cytometry to enumerate B and T cells should be performed at least six weeks apart when the patient is clinically well. CD4+ T cells exhibit diurnal variability and changes of up to 50% in total CD4+ T cell numbers can occur.<sup>38-40</sup> It is standard practice in other immunosuppressed patients (patients with HIV) that CD4+ T cell counts should be done at consistent times of the day. Single platform flow cytometry technology gives more reproducible results than the analysis of lymphocyte subsets using a total lymphocyte count from a haematology Coulter counter.<sup>41</sup> Further immunological investigation would be dependent on both the concentration of IgG and the expertise of the regional immunology laboratory. If the serum IgG is greater than 3.0 g/litre, the measurement of specific antibodies to a panel of protein and carbohydrate antigens (tetanus, diphtheria, pneumococcus, and haemophilus) should be undertaken. Failure to mount adequate antibody responses after test immunisation in a patient with a history of recurrent infections would be an indication to start immunoglobulin replacement treatment. Some immunologists assess the presence of IgG antibody to common childhood viral infections such as measles, mumps, rubella, herpes simplex, and herpes zoster. Absent antibody responses to these viruses, despite a history of childhood infection or immunisation (measles, mumps, rubella), may suggest the presence of antibody deficiency. In addition, IgG antibodies to CMV and toxoplasma should be sought to determine whether an individual is at risk of reactivated infection with these organisms. CMV viral load has been shown to determine the risk of opportunistic infection with this organism in patients with bone marrow and solid organ transplants and HIV infection.<sup>42</sup> This technology probably provides similar important prognostic information in Good's syndrome, although there are no studies supporting the use of this technique in this patient group. In individuals with an IgG concentration less than 3.0 g/litre, serology is not reliable and the detection of viral or protozoan antigens using the polymerase chain reaction should be undertaken for organisms where this technology is available. T cell proliferative responses to PHA and interleukin 2 (IL-2)/OKT3 should be performed using at least three different mitogenic concentrations. Both absolute values and the stimulation index

should be reported in conjunction with results from a healthy individual control. We would argue that the proliferative data should be expressed both in terms of absolute counts per minute (cpm) and cpm/T cell number to allow for differences in T cell counts between the patient and the healthy control. The report should indicate whether T cell proliferation is normal, reduced, or absent.

"T cells isolated from patients with thymoma can inhibit immunoglobulin production by B cells and pre-B cell growth in healthy controls"

T cell counts and mitogen responses do not readily predict the risk of opportunistic infections (CMV in particular) in Good's syndrome. In addition, some patients need immunosuppressive medication to treat autoimmune complications of a thymoma so that there is a need for a novel immunology test to assess the degree of immunosuppression in this patient group. New developments in immunological techniques, such as ELISPOT technology,<sup>43-45</sup> major histocompatibility complex class I tetramers,<sup>46-47</sup> and the detection of cytokines using intracellular flow cytometry,<sup>48-49</sup> may have a potential role in the future to assess the risk of opportunistic infections in patients with Good's syndrome. A systematic study of the use of different technologies to assess antigen specific T cell responses is needed to determine whether this approach would identify those individuals at increased risk of systemic CMV infection so that prophylactic treatment could be offered.

The pathology of Good's syndrome suggests at least two possible pathogenic mechanisms for the association of antibody deficiency with thymoma. The first explanation is that cytokines, possibly secreted by bone marrow stromal cells, may influence both thymic and B cell precursor growth and differentiation. Indirect evidence for this statement comes from murine studies, which show that limitin, an interferon-like cytokine produced by a bone marrow stromal cell line, preferentially inhibits precursor B cell growth and differentiation.<sup>50</sup> In addition, supernatants from a murine thymic stromal cell line can promote the growth of a pre-B cell line,<sup>51</sup> which suggests that the thymus may have the potential to influence precursor B cell growth and maturation. The recent identification of a thymic epithelial stem cell population<sup>52-53</sup> will facilitate studies into the signals required for thymic stem cell expansion and the differentiation of thymic epithelial cells, with potential clinical application for peripheral T cell expansion, understanding of the genetic basis of thymoma, and the identification of potential growth or inhibitory factors that the thymus may share with other cell populations, such as bone marrow stromal cells or B cells. A second explanation for the immune deficiency associated with thymoma comes from studies of paraneoplastic phenomena in thymoma, such as pure red cell aplasia, which show that T cells or autoantibodies can directly or indirectly inhibit erythropoiesis.<sup>54</sup> T cells isolated from patients with thymoma can inhibit immunoglobulin production by B cells<sup>55</sup> and pre-B cell growth<sup>56</sup> in healthy controls. The identification of markers associated with regulatory T cells<sup>57-60</sup> may provide further insights into the relations between these cell populations (if any) and the development of antibody deficiency in patients with thymoma. Finally, a large number of patients with Good's syndrome experience opportunistic infection associated with defects in cell mediated immunity. Further studies should clarify whether such patients have a loss in either the naïve or memory CD4+ T cell population. The clinical application of these findings is that one might try to restore immunity in patients with extremely low numbers of CD4+ T cells using cytokines, such as IL-7, which promote the growth and development of naïve T cells,<sup>61</sup> or IL-2 alone, IL-2 and granulocyte-macrophage colony stimulating factor, or IL-12,<sup>62</sup> which expands the numbers of memory T cells.

## MANAGEMENT OF GOOD'S SYNDROME

An anterior mediastinal mass is noted on a postero-anterior chest x ray in 80% of patients with thymoma.<sup>65</sup> Lateral x ray views may delineate the outline of the mass. Thymomas can be a subtle feature on chest x rays, and in one study 25% of tumours were missed, with a diagnostic delay of 41 months.<sup>65</sup> Hence, a computed tomography (CT) scan of the chest should be requested if the clinical suspicion of thymoma is high, despite absent findings on chest x rays. CT scans of the chest can define the extent of a thymoma and clinically stage this tumour.<sup>64, 65</sup> In addition, a CT scan may outline the presence of bronchiectasis, which identifies a subgroup of patients who need close liaison with chest physicians, postural drainage, prophylactic antibiotics, and perhaps more intensive immunoglobulin treatment.<sup>66</sup> The potential risk of radiation damage in patients with antibody deficiency syndromes<sup>67</sup> may be investigated with techniques such as magnetic resonance imaging, which is equivalent to CT in staging this disease.<sup>64</sup> The histology of thymoma in Good's syndrome is usually a spindle cell variant, and malignant thymic carcinomas are uncommon in this condition.<sup>68</sup> Other histological variants of thymoma, such as epithelial cell tumours or mixed epithelial/lymphoid tumours, have also been noted.

The treatment of thymoma is surgical removal or debulking of the tumour,<sup>10, 65, 68</sup> and the most important indicator of long term prognosis is completeness of tumour resection.<sup>65, 69</sup> Patients with advanced stage 3 or stage 4 disease tumours often require radiotherapy and combination chemotherapy. Although there are no systematic studies of surgical resection or multimodality treatment in patients with Good's syndrome, we think that the principles of management of thymoma should also apply to this patient subgroup, although removal of the thymoma does not reverse the immunological abnormalities. Antibody deficiency requires immunoglobulin replacement treatment. A retrospective review of the efficacy of immunoglobulin treatment in this disorder showed that 23 of 30 patients had a reduction in the numbers of bacterial sinopulmonary infections.<sup>6</sup> Poorer responses were seen in those with intramuscular immunoglobulin replacement. Patients with Good's syndrome who are CMV antibody negative or whose CMV serology is unknown, or cannot be determined, should receive CMV negative blood to avoid the potential risk of iatrogenic disease.<sup>35</sup> Graft versus host disease is a complication of malignant thymoma and it would be prudent to use irradiated blood in patients with Good's syndrome.<sup>70, 71</sup>

"The treatment of thymoma is surgical removal or debulking of the tumour, and the most important indicator of long term prognosis is completeness of tumour resection"

## PROGNOSIS

The prognosis in patients with Good's syndrome is believed to be worse than in those with XLA and CVID. In a single centre review of primary antibody deficiency spanning 20 years, 70% of patients with Good's syndrome were alive five years after diagnosis compared with almost 100% of patients with XLA and CVID.<sup>72</sup> At 10 years, only 33% were alive compared with 95% of patients with XLA and CVID. The principal causes of death are as a result of infection, autoimmune disease, or the haematological complications of this condition. Thymoma itself is not believed to contribute towards excess mortality in this condition.

## CONCLUSIONS

Good's syndrome should be considered in patients over 40 years of age with unexplained antibody deficiency. The most

## Take home messages

- Good's syndrome (thymoma with immunodeficiency) is a rare cause of combined B and T cell immunodeficiency in adults
- The clinical characteristics of Good's syndrome are increased susceptibility to bacterial infections with encapsulated organisms and opportunistic viral and fungal infections
- Defects in cell mediated immunity are important causes of morbidity and mortality in this disorder and opportunistic infections such as mucocutaneous candida, cytomegalovirus infection, and *Pneumocystis carinii* pneumonia in patients with presumed common variable immune deficiency should alert the clinician to consider Good's syndrome
- The main findings on investigation of the immune system are hypogammaglobulinaemia, low or absent B cells, and variable defects in cell mediated immunity, such as CD4+ T cell lymphopenia and reduced T cell mitogen proliferative responses
- Treatment of Good's syndrome involves resection of the thymoma and immunoglobulin replacement to maintain adequate trough IgG values
- A high index of suspicion and appropriate microbiological investigations are required to diagnose and treat opportunistic infections

consistent immunological abnormalities are hypogammaglobulinaemia and reduced or absent B cells. The formation of a Good's syndrome disease register under the auspices of the UK Primary Immunodeficiency Network or the European Society for Immune Deficiencies would provide a framework for the systematic study of the immune defect in this condition.

## LITERATURE SEARCH

Published data for this review were identified by searching MEDLINE. The search terms included: thymoma with immunodeficiency, Good's syndrome, thymoma, and infection. References from papers identified in the MEDLINE search were identified and searched for the presence of reported immunological abnormalities in thymoma. Only papers or abstracts published in English were included.

## Authors' affiliations

**P Kelleher**, Department of Immunology, St Mary's Hospital, Praed Street, London W2 1NY, UK

**S A Misbah**, Department of Immunology, Oxford Radcliffe NHS Trust, John Radcliffe Hospital, Oxford OX3 9DV, UK

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