Good Syndrome: An Adult-Onset Immunodeficiency Remarkable for Its High Incidence of Invasive Infections and Autoimmune Complications

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Background. Good syndrome (GS) is a rare condition in which thymoma is associated with hypogammaglobulinemia. It is characterized by increased susceptibility to bacterial, viral, and fungal infections, as well as autoimmunity. Most patients have no circulating B cells.

Methods. The French DEFicit Immunitaire de l’adulte cohort provides detailed clinical and immunological descriptions of 690 adults with primary hypogammaglobulinemia. Comparisons between patients with GS, those with common variable immunodeficiency (CVID), and those with B− CVID (circulating B cells <1%) were performed.

Results. Twenty-one patients had GS and 440 had CVID, including 39 B− CVID (circulating B cells <1%) patients. Invasive bacterial infections were observed in 90.5% of GS, 54% of CVID, and 72% of B− CVID patients. Eight patients with GS had opportunistic infections, despite normal peripheral CD4+ T-cell numbers. Autoimmune complications were demonstrated in 76% of GS, 29% of CVID, and 26% of B− CVID patients. The spectrum of autoimmunity in GS was uncommon, consisting of oral lichen planus, graft-vs-host disease–like colitis, and pure red cell aplasia, different from the pattern observed in CVID patients. GS patients did not display lymphoid hyperplasia nor lymphoma, unlike those with CVID or B− CVID.

Conclusions. GS differs notably from CVID and B− CVID: very late onset, no familial cases, and absence of lymphoid hyperplasia. The key observation is the very high frequency of invasive bacterial infections in GS, an issue that physicians should be aware of.

Keywords. Good syndrome; thymoma; infection; autoimmunity; CVID.
with autoimmune disorders, mostly myasthenia gravis (30%–50%) [8]. Less frequently, hypogammaglobulinemia develops to form the so-called GS (0.2%–6% of thymomas) [3, 9]. The pathogenesis of this immunodeficiency remains elusive. Notably, hypogammaglobulinemia is not corrected following thymus removal.

To date, <200 patients with GS have been reported in the literature; most cases are isolated case reports, the largest series reporting only 5 patients [4, 6].

The prospective French DEFicit Immunitaire de l’adulte (DEFI) series of adult patients with primary hypogammaglobulinemia enrolled 21 patients with GS recruited on the basis of hypogammaglobulinemia associated with thymoma regardless of clinical phenotype. Their clinical and biological features were compared with patients with common variable immunodeficiency (CVID) and B− CVID (circulating B cells <1%) [10].

PATIENTS AND METHODS

Patients

DEFI is a French national study of adults with primary hypogammaglobulinemia (serum immunoglobulin G [IgG] level <5 g/L, and/or immunoglobulin A [IgA] < 0.7 g/L, and/or immunoglobulin M [IgM] < 0.4 g/L, and/or IgG subclass deficiency) including GS. The study was approved by the local ethics committee, and all patients gave written informed consent [11]. A total of 690 patients with primary hypogammaglobulinemia were enrolled by 47 centers between April 2004 and June 2013. For each patient, infectious, autoimmune, lymphoproliferative, or tumoral complications were compiled in a clinical file along with family medical history. A blood sample collected on the day of enrollment was used to perform detailed centralized B-cell and T-cell phenotyping.

Originally, GS was defined as thymoma with hypogammaglobulinemia. In this study, we considered all patients with thymoma and an antibody production defect, if this affected any class or subclass of immunoglobulin, as having GS.

CVID diagnostic criteria were consistent with those of the European Society for Immunodeficiencies/Pan American Group for Immunodeficiency. CVID patients with a low number of circulating B cells (<1%) were referred to as B− CVID according to the EuroClass classification [11]. Because GS patients usually do not have circulating B cells, we used B− CVID patients from the DEFI cohort as a comparison group. Comparison with the whole group of 440 CVID patients was also performed.

Statistical Analysis

Descriptive statistics were reported as median (interquartile range [IQR]) or number (%). Characteristics of GS patients were compared to those of B− CVID and CVID patients included in the DEFI study during the same period of time, but no statistical test was performed for the comparison of patient characteristics due to small sample sizes. Overall survival was calculated from hypogammaglobulinemia diagnosis until the last visit or death from any cause. Follow-up ended in June 2014. Survivals were estimated using the Kaplan–Meier product-limit method. For overall survival comparison, the groups were GS, B− CVID, and B+ CVID, and the log-rank test was used. The B+ CVID group was defined as CVID patients with B cells >1% (ie, excluding B− CVID). Statistical analysis was conducted using Stata Statistical Software version 11.1 (StataCorp, College Station, Texas).

RESULTS

Clinical Features

Among the 690 patients included in the DEFI study, 21 patients (3%) met the criteria for GS and 440 patients were considered as having CVID, including 39 belonging to the B− CVID group.

Main clinical characteristics of the GS patients are provided in Table 1. There were 9 women and 12 men, and no family cases were reported. Median age at first symptoms, at diagnosis of hypogammaglobulinemia, and at evaluation was 56, 60, and 64 years, respectively, for GS. Thymoma was diagnosed before hypogammaglobulinemia in 7 patients (with an interval of 2–17 years), within the same year in 12 patients, and following hypogammaglobulinemia diagnosis in 2 patients (with an interval of 2–8 years). Nineteen of 21 patients had undergone thymectomy before evaluation, with a median time of 3.4 years (IQR, 2–13 years).

Overall, 20 patients (95%) had infectious complications. Pneumonia was reported in 18 patients (86%). Streptococcus pneumoniae was documented in 7 patients (33%) and Haemophilus influenzae in 6 patients (29%). Bacteremia was reported in 9 patients (43%), with gram-negative bacilli in 6 of them. Recurrent bronchitis and sinusitis were noted in 12 (57%) and 7 (33%) patients, respectively. Eight patients (38%) developed bronchiectasis. At the time of evaluation, 13 patients (61%) were receiving replacement immunoglobulin therapy, 17 (81%) had required antibiotics, and 14 (67%) had been hospitalized during the 12-month period prior to inclusion in the study.

Eight patients developed infections suggestive of a cellular immune defect: 5 patients had mucosal candidiasis (3 recurrent oral thrush, 1 esophageal candidiasis, 1 chronic mucocutaneous candidiasis); 4 had cytomegalovirus (CMV) disease associated, respectively, with mucosal candidiasis, aspergillosis, isosporosis, or disseminated Mycobacterium tuberculosis. None of these patients had a CD4 T-cell count <250 × 10⁶ cells/L nor were receiving immunosuppressive therapy at the time of assessment.
Chronic diarrhea was noted in 8 patients (38%), with documentation of Campylobacter species in 4 cases (19%), Salmonella in 2 cases, Shigella in 1 case, and CMV colitis in 1 patient. One patient experienced herpes simplex virus esophagitis; another had villous atrophy. Nodular regenerative hyperplasia of the liver was reported in 1 patient.

Autoimmunity was demonstrated in 16 patients (76%). Oral lichen planus (OLP) was noted in 10 patients (48%). Six of them had chronic diarrhea, with a documented graft-vs-host disease–like inflammatory bowel disease in 4. OLP vanished after thymus removal in 2 patients, and colitis healed after thymus removal in 1 patient. One patient had associated alopecia areata. Pure red cell aplasia (PRCA) was reported in 7 patients (33%); this recovered after thymectomy without additional immunosuppressive treatment in 1 patient in whom previous intravenous immunoglobulin infusion (1 g/kg for two days) had had no effect. Cyclosporine was effective for PRCA in 2 patients. Five patients (24%) had neutropenia, and 1 patient had autoimmune hemolytic anemia. Only 1 patient had myasthenia gravis, which persisted after thymectomy. Autoimmunity presented after thymectomy in 2 patients and disappeared after thymectomy in 4 patients. Eight patients (38%) had >1 autoimmune disorder.

Clinical characteristics between patients with GS, those with B− CVID, and the total cohort of CVID patients are provided in Table 2. GS patients were older at onset of symptoms. They were more prone to severe bacterial infections (pneumonia, bacteremia) compared with B− CVID or CVID patients. GS patients did not display lymphoid hyperplasia, granuloma, or lymphoma, as opposed to B− CVID or CVID.
patients. A single patient had splenomegaly, but this was in the context of autoimmune hemolytic anemia.

**Biological Features**

Fourteen patients had defects affecting all 3 classes of immunoglobulin. Four patients had IgG1 or IgG2 subclass defect associated with decreased IgM and IgA, 2 patients had IgG1 or IgG2 subclass defect with decreased IgM but normal IgA levels, and 1 patient had decreased IgG and IgA but normal IgM levels. The number of patients with IgG < 5 g/L, IgA < 0.7 g/L, or IgM < 0.4 g/L was 13 (62%), 18 (86%), and 19 (90%), respectively. Median serum IgG, IgA, and IgM level at diagnosis was, respectively, 3.35 g/L (IQR, 1.99–5.64 g/L), 0.14 g/L (IQR, 0.07–0.43 g/L), and 0.17 g/L (IQR, 0.09–0.22 g/L). No monoclonal gammopathy was detected.
CD19+ B cells were <1% of total lymphocytes (<20 × 10^6/L) in 20 patients. Only 1 patient was an outlier with 140 × 10^6/L CD19+ B cells, 93% of them being immunoglobulin D (IgD)+ CD27− naive B cells, only 1% being IgD−CD27+ switched memory B cells.

Comparison of immunoglobulin levels between GS, B− CVID, and CVID patients did not show significant differences (Figure 1).

The median CD4+ T lymphocyte count was 404 × 10^6 cells/L (IQR, 340–714) in GS patients, 575 × 10^6 cells/L (IQR, 313–778) in B− CVID patients, and 842 × 10^6 cells/L (IQR, 413–842) in CVID patients.

The proportion of naive CD45RA−CCR7−CD4+ T lymphocytes was 43% (IQR, 29%–55%) in GS patients, 14% (IQR, 4%–39%) in B− CVID patients, and 25% (IQR, 10%–40%) in CVID patients. The CD4+CD127low T-regulatory lymphocyte count was available for 13 patients with GS, 14 patients with B− CVID, and 242 patients with CVID. Median count was 6.2% (IQR, 4.4%–7.9%) in GS patients, 4.4% (IQR, 2%–7.3%) in B− CVID patients, and 6.5% (IQR, 4%–8.4%) in CVID patients.

**Outcome**

Seven patients died, 3, 4, 6, 18, 18, 21, and 26 years, respectively, after hypogammaglobulinemia diagnosis (n = 2), other infection (n = 4), or brain cancer (n = 1). Overall survival for 21 GS, 39 B− CVID, and 401 B+ CVID patients is shown in Figure 2. Overall survival at 10 years was 84% (95% confidence interval [CI], 49%–96%) in GS patients, 86.5% (95% CI, 68%–95%) in B− CVID patients, and 97% (95% CI, 95%–98%) in B+ CVID patients (log-rank P < 10^-4).

**DISCUSSION**

To our knowledge, this is the largest series on GS ever reported, and the frequencies of associated characteristics observed in this study are likely to be informative, not being skewed by bias linked to unusual complications as in case reports. In this study, 21 GS patients were enrolled, together with 440 CVID patients. Assuming a prevalence of 1 per 25 000 for CVID, we estimate GS prevalence to be approximately 1 per 500 000. The main input of our study is to emphasize the very high frequency of invasive bacterial infections in GS patients (90.5%), which is remarkably higher than in the literature. Opportunistic infections occurred despite relatively conserved CD4+ T-cell counts and at a relatively similar frequency as that previously reported in a literature review (5/21 vs 16/51 by Tarr et al [4]). It is of interest that the risk and spectrum of infections is relatively different from that observed in non-GS thymoma patients, in whom overall infections are less frequent (15/29 [52%]), with only 3 of 29 (10%) severe bacterial infections and 6 of 29 (20%) opportunistic infections (5 esophageal candidiasis, 1 progressive multifocal leukoencephalopathy) [12]. Compared with B− CVID patients, GS patients display more frequent invasive bacterial infections, whereas immunoglobulin supplementation is less frequent.

In our study, use of immunoglobulin infusions at evaluation was recorded in only 13 of 21 patients, which is comparable to immunoglobulin use in GS in the literature (30/51 in Tarr et al [4]) but surprising, given the high frequency of invasive infections. Notably, IgM levels are relatively conserved in many GS patients, which could explain the low immunoglobulin substitution rate. On the other hand, IgM levels are decreased in most patients, and this may account for increased susceptibility to invasive encapsulated bacterial infections. Better prophylaxis could be offered by vaccination against encapsulated bacteria and/or antibiotics. In 1 patient with undetectable serum IgM but relatively conserved IgG (6 g/L), 23-valent pneumococcal polysaccharide vaccination was associated with protective antibody titers at 4 years, in the absence of immunoglobulin replacement therapy (data not shown). However, regarding the high level of invasive bacterial infections in those patients, immunoglobulin substitution should be considered despite quite conserved serum IgG levels. In addition, the frequent intestinal mucosal inflammation might contribute to the high rate of invasive infections.

Autoimmunity is a recognized feature in thymoma. In the single-center retrospective study from Holbro et al on 29 patients with thymoma (including only 3 patients known to display hypogammaglobulinemia), autoimmunity was observed in 16 of 29 patients (55%) [12]. Myasthenia gravis (10 of 29 patients) was the most frequent autoimmune disease. Additional entities included pemphigus, PRCA, OLP, Sjögren syndrome, and systemic lupus erythematosus (n = 2 each). Six of 29 patients (21%) had >1 autoimmune disorder. We observed a higher frequency of autoimmune complications in GS (76%) and, interestingly, a different pattern. In patients with GS, chronic inflammatory mucosal disease (mostly OPL but also
inflammatory bowel disease) is observed with high frequency, while only occasionally reported in unselected thymomas (2/172 in Gibson et al [13]). PRCA is also frequent, whereas myasthenia gravis is rare. In our series, most autoimmune complications arose before thymectomy, and only a few of them resolved after thymectomy. Neoplastic thymoma epithelial cells lack expression of autoimmune regulator (AIRE) [14, 15]. Loss of AIRE expression leads to both defective negative selection and abnormal thymic architecture, resulting in an aberrant thymic microenvironment [16, 17]. This may promote activation of maturing thymocytes against locally expressed autoantigens. Pathogenic autoantibodies are common in thymoma, mostly maturing thymocytes against locally expressed autoantigens. microenvironment [16, 17]. This may promote activation of maturing thymocytes against locally expressed autoantigens. Pathogenic autoantibodies are common in thymoma, mostly anti-acetylcholine receptor antibodies causing myasthenia gravis, although a wide range of anticytokine autoantibodies are also described [18–21]. In the study from Burbelo et al on 17 patients with thymoma, all patients with opportunistic infection showed multiple anticytokine autoantibodies (mainly interferon (IFN) α, IFN-β, interleukin [IL] 1α, IL-12, IL-17A) with blocking activity in vitro, suggesting that anticytokine autoantibodies may be important in the pathogenesis of adult-onset immunodeficiency associated with thymoma in these patients [19].

Except for autoimmunity, patients with GS do not display noninfectious complications such as lymphoid hyperplasia, granuloma, chronic liver disease, or enteropathy with villous atrophy, which are classical disease-related complications seen in CVID and other primary immunodeficiencies. The later onset compared to CVID and the absence of family cases suggests that GS may be an acquired disorder. Given the particular spectrum of associated autoimmune complications in GS, one could speculate that the hypogammaglobulinemia might be another autoimmune feature. As 1 of our GS patients had normal circulating B cells, there might be different mechanisms leading to hypogammaglobulinemia in thymoma patients. GS was not associated with any particular thymoma subtype according to the World Health Organization classification, nor to specific human leukocyte antigen haplotypes (data not shown).

In conclusion, GS strikingly differs from CVID and B−CVID in terms of its very late onset, lack of familial cases, and absence of lymphoid hyperplasia, suggesting that GS might be an acquired immunodeficiency, part of an increasingly recognized group of adult-onset immunodeficiency disorders associated with thymoma. However, given the specific characteristics—namely, the very high frequency of invasive bacterial infections and the particular autoimmune spectrum—it is still relevant to distinguish patients with GS from other patients with adult-onset immunodeficiency associated with thymoma.

Notes

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