Review Article

Characteristics of Good's Syndrome in China: A Systematic Review

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Abstract

Background: Good's syndrome (GS) is a rare disease characterized by thymoma, hypogammaglobulinemia, low or absent B-cells, decreased T-cells, an inverted CD4+/CD8+ T-cell ratio and reduced T-cell mitogen proliferative responses. GS is difficult to diagnose preoperatively due to its rarity and lack of typical symptoms, the characteristics of Chinese GS patients are still lacking. This study aimed to systematically review all the clinical, laboratory, and immunologic findings of reported cases of Chinese patients with GS.

Methods: We searched for case reports and articles up to January 2017 using PubMed, China National Knowledge Infrastructure, Wangfang database and China Science and Technology Journal Database with the following words in combinations as key words: "thymoma," "hypogammaglobulinemia," and "Good's syndrome." The text words and MeSH terms were entered depending on the databases characteristics. The reference lists from retrieved articles were also screened for additional applicable studies. The authors were restricted to Chinese. There was no language restriction.

Results: Forty-seven patients were reported in 27 studies. We found that GS has a nationwide distribution and that most cases (83%) have been described on the mainland of China. The initial clinical presentation is varied, ranging from symptoms related to the thymoma to infections resulting from immunodeficiency. Type AB (50%) is the most common histologic type of thymomas in Chinese GS patients according to the World Health Organization classification of thymomas. With respect to infection, sinopulmonary infection (74%) is the most common type, followed by skin infection (10%) and intestinal tract infection (10%). Diarrhea was presented in 36% of patients, and autoimmune manifestations were presented in 36% of patients.

Conclusions: GS is a rare association of thymoma and immunodeficiency with a poor prognosis. Astute clinical acumen and increased awareness of the clinical and immunological profile of GS are needed to increase early diagnosis, that would benefit improved therapeutic effects.

Key words: Agammaglobulinemia; Diarrhea; Good's Syndrome; Immunologic Deficiency Syndromes; Thymoma

Introduction

Good's syndrome (GS) is a rare disease which is difficult to diagnose preoperatively and is characterized by thymoma, hypogammaglobulinemia, low or absent B-cells, decreased T-cells, an inverted CD4+/CD8+ T-cell ratio and reduced T-cell mitogen proliferative responses.[1] GS was first reported by Robert Good in 1954.[2] The main clinical manifestations include thymoma, infection, and gastrointestinal manifestations (such as diarrhea) and autoimmune manifestations (such as myasthenia gravis, pure red cell aplasia (PRCA), and oral lichen planus). GS sporadic worldwide, with 46.9% of cases reported in Europe, 29.5% reported in America, 22.8% reported in Asia, 0.4% reported in Africa, and 0.4% reported in Oceania.[1] However, GS is difficult to diagnose due to its rarity and lack of typical symptoms, and the characteristics of Chinese patients remain unclear. Therefore, we systematically reviewed the literature and summarize the characteristics of Chinese GS patients to improve the diagnosis rate of GS.

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Methods

Search strategy

We searched for all cases and articles up to January 2017 using the PubMed, China National Knowledge Infrastructure database, Wangfang database and China Science and Technology Journal Database with the following words in combinations as key words: "thymoma," "hypogammaglobulinemia," and "Good's syndrome." The text words and MeSH terms were entered depending on the databases characteristics. The reference lists from retrieved articles were also screened for additional applicable studies. We considered completed published studies as well as abstracts presented at meetings. Authors of relevant studies were contacted regarding unpublished cases. The authors were restricted to Chinese. There was no language restriction. The flowchart of the review search and identification is shown in Figure 1.

Inclusion and exclusion criteria

Since there were a number of definitions for GS, we defined GS as a constellation of thymoma and adult-onset immunodeficiency characterized by hypogammaglobulinemia, low or absent B-cells, variable defects in cell-mediated immunity with a CD4+ T lymphopenia, an inverted CD4+/CD8+ T-cell ratio and reduced T-cell mitogen proliferative responses according to Kelesidis and Yang definition.[1] We included cases and observational studies that reported GS, regardless of publication status.

Study selection

Two authors independently scanned the titles, authors, and abstracts of the reports to identify eligible articles. We attempted to locate the full text if we could not judge whether an article was in keeping with the inclusion and exclusion criteria. Any disagreement was resolved by discussion; a third reviewer was consulted if we could not reach a consensus.

Results

Study identification

Thirty studies were identified after screening the titles, abstracts, and authors,[3-32] four of which were excluded (two did not qualify as diagnoses of GS,[10,25] whereas the other two[3,29] were excluded because they reported the same patients as other studies[5,15]). An unpublished case report of GS was also included.[33] Finally, 47 patients were reported in 27 studies. Thirty-nine (83%, 39/47) patients were reported in the mainland of China, five (11%, 5/47) in Taiwan (China), three (6%, 3/47) in Hong Kong (China). Sixteen (59%, 16/27) studies were published in Chinese, and 11 were published in English

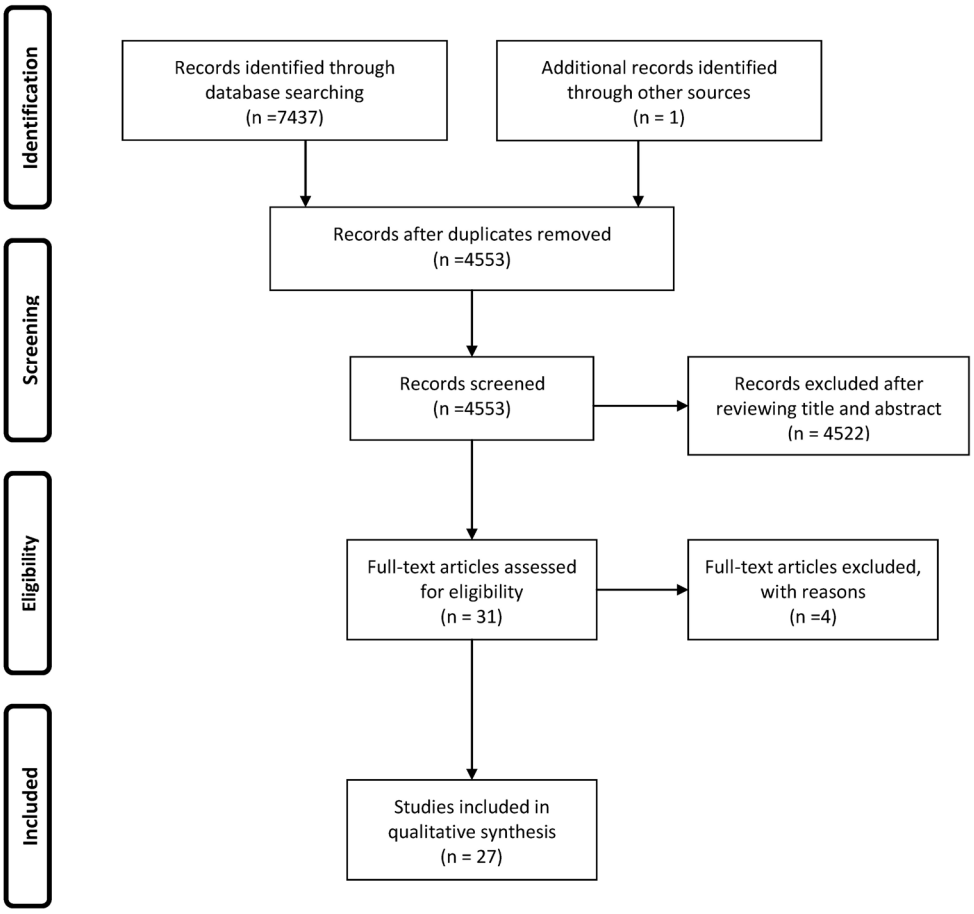

Figure 1: Flowchart of the review search and identification.

(41%, 11/27). Among these, 5 were from Taiwan (China), 3 were from Hong Kong (China) and 3 were from the mainland of China.

There were 31 female patients and 16 male patients, who had a mean age of 55.2 years (range, 28–77 years, although one of the studies did not provide the patient's age). The interval between developing symptoms and a diagnosis of GS was 5 days to 11 years.

Clinical manifestations of Good's syndrome

Thymoma

Thirty-five patients reported the sequence between thymoma and other symptoms. The diagnosis of thymoma preceded the emergence of other symptoms in nine (26%, 9/35) patients, followed the emergence in 19 (54%, 19/35) patients, and was almost simultaneous in seven (20%, 7/35) patients.

Eleven patients did not receive thymectomy, we summarized the histologic types of thymomas among the remaining 36 patients, the histologic type of thymoma in three patients were according to traditional classification (one was lymphocytic type, the other two were mixed cell type), 28 patients were according to the World Health Organization (WHO) classification [Table 1], and five patients were not specified.

Infections

Infection is the most common symptom of GS. We summarized the infection sites and pathogens of Chinese GS patients in Table 2. No infections were reported in five patients.

Table 1: Histologic type of thymomas in Chinese patients with GS according to the WHO classification (n = 28)

Histologic type of thymoma	Number of cases, n (%)
Type AB	14 (50)
Type A	10 (36)
Type B2	2 (7)
Type B3	1 (4)
Malignant thymoma	1 (4)

GS: Good's syndrome; WHO: World Health Organization.

Gastrointestinal manifestations

Diarrhea was present in 36% (17/47) of patients. Infection is one of the causes, but not the main cause.

Autoimmune manifestations

Seventeen patients (36%, 17/47) presented autoimmune manifestations. We summarized the autoimmune manifestations of the 17 patients in Table 3.

Laboratory data

The laboratory findings in patients with GS were presented in Table 4.

Other manifestations

Hearing loss was presented in four patients, one of them due to frequentative auditory tube infection, the other three without definitive cause.

Discussion

GS was classified as a distinct entity involving primary immunodeficiencies in 1999 by the expert committee of the WHO and International Union of Immunological Societies.[34] Its peak incidence is between the ages of 40 and 50 years.[35] Foreign literatures report males and females are equally affected, but we found females are more inclined to suffer GS in Chinese patients. GS can also occur in children, although this is extremely rare.[36]

The pathogenesis of GS remains unknown. There are two possible mechanisms for the association between hypogammaglobulinemia and thymoma.[37] The first is that cytokines secreted by bone marrow stromal cells might influence the growth and differentiation of both thymic and B-cell precursors. The second is that T-cells isolated from patients with thymoma might inhibit pre-B-cell growth and immunoglobulin production by B-cells. However, neither hypothesis is widely accepted.

The diagnosis of thymoma might occur preceding, after or simultaneously with other clinical manifestations. Patients might complain of symptoms that are secondary

Table 2: Infections described in 42 Chinese patients with GS

Infection	Number of patients*	Pathogens	Number of patients
Sinopulmonary infection	31	CMV	7
Skin infection	4	*Pseudomonas aeruginosa*	5
Intestinal tract infection	4	*Pneumocystis carinii* pneumonia	4
Eye infection	2	*Klebsiella pneumoniae*	3
Encephalitis	2	Herpes zoster	3
Urinary tract infection	1	*Staphylococcus aureus*	2
Spontaneous peritonitis	1	*Clostridium difficile*	2
Joint infection	1	*Herpes simplex*	1
Intra-abdominal infection	1	*Mucor*	1
Carbuncle	1	Tuberculosis	1
Cellulitis	1	*Toxoplasma gondii*	1
Viremia	1	*Staphylococcus*	1
		Escherichia coli	1
		Haemophilus influenzae	1

*Some patients suffered more than one site infection. CMV: *Cytomegalovirus*; GS: Good's syndrome.

Table 3: Autoimmune manifestations described in 17 Chinese patients with GS

Autoimmune manifestation	Number of patients, *n*
PRCA	8*
Myasthenia gravis	3
Lichen planus	2
Myelodysplastic syndrome	1
Monoclonal gammopathy	1
Myositis	1
leukoderma	1
Polycythemia vera	1

*One patient suffered PRCA and lichen planus simultaneously. PRCA: Pure red cell aplasia; GS: Good's syndrome.

Table 4: Laboratory findings in patients with GS with available data

Laboratory data	Number of patients with available data (*n*/*N*, %)
Low or absent peripheral B-cells	42/42 (100)
Low CD4+ T-cell count	37/39 (95)
Normal CD4+ T-cell count	2/39 (5)
High CD8+ T-cell count	7/14 (50)
Normal CD8+ T-cell count	6/14 (43)
Low CD8+ T-cell count	1/14 (7)
CD4+/CD8+ T-cell ratio reversed	41/42 (98)
Low NK-cell count	12/13 (92)
Normal NK-cell count	1/13 (8)
Leukopenia	12/22 (55)
Normal white cell count	5/22 (23)
Leukocytosis	5/22 (23)
Anemia	13/36 (36)
Hypogammaglobulinemia	45/45 (100)
Low IgG, IgM, and IgA	39/45 (87)
ANA positive	1/8 (13)

ANA: Antinuclear antibody; GS: Good's syndrome; NK: Natural killer.

to the thymoma. Superior vena cava syndrome, Horner's syndrome, and masses in the neck have also been reported as initial manifestations. The most common histologic types of thymoma in GS is the AB variant (WHO classification),[1] which is in accordance with our study. Thymoma can be diagnosed by posteroanterior chest X-ray, which has a detection rate of 80%.[38] Because the features of thymoma on chest X-rays may be subtle, in one study, 25% of tumors were missed, with a diagnostic delay of 41 months.[38] Therefore, a CT scan of the chest is recommended when a clinician is highly suspicious of thymoma, even the X-ray is negative. As the association between thymoma and immunodeficiency is not generally well known, it may be advisable to measure quantitative immunoglobulin levels in all patients with thymoma to diagnose and treat at an early stage the 3–6% who have or will develop GS.[39,40] In this study, we found the diagnosis of thymoma followed the emergence of other symptoms in more than a half of patients. Therefore, we suggest doctors conduct relevant examinations to detect thymoma in patients with hypogammaglobulinemia and decreased peripheral blood lymphocytes.

Due to both humoral and cell-mediated immune deficiencies, GS patients can easily contract various infections, including bacterial, fungal, viral, and other opportunistic infections. For bacterial infections, recurrent infections of the upper and lower respiratory tract are the most common,[1,39] with common pathogens including *Haemophilus influenzae*, *Pseudomonas* spp., and *Klebsiella* spp.[1] Bronchiectasis might also develop in GS patients. Among fungal infections, Kelesidis and Yang reported *Candida* is the most common pathogen,[1] but we found *Pneumocystis jirovecii* is more common. Among viral infections, *Cytomegalovirus* (CMV) is the most common pathogen reported, we confirm the conclusion in this study. Opportunistic infections such as viral and fungal infections suggest GS patients have severe defects in cell-mediated immunity. Interestingly, unlike HIV-infected patients, opportunistic infection by *Mycobacterium tuberculosis* has been uncommonly described in GS. To the best of our knowledge, only six cases reported cases of GS included *M. tuberculosis* infection.[1,19,41-43]

A total of 32–43% of patients present with diarrhea, which is chronic in most cases.[1,39] Approximately one-third (36%) of patients have infectious diarrhea. *Salmonella* spp. are the most common pathogen, and *Giardia lamblia* and CMV have also been occasionally isolated.[1] Besides, we also found *Clostridium difficile* might also be a potential pathogen. The mechanism by which hypogammaglobulinemia causes diarrhea is unclear, but it has been postulated that it may be related to malabsorption, which may be caused by mucosal lesions resembling villous atrophy, and it may be resolved by reinstatement of immunologic status.[44,45]

A variety of autoimmune manifestations might present in GS patients, the most common of which is PRCA, followed by myasthenia gravis. A systematic review suggested that autoantibodies can be detected in more than half (56%) of patients with GS, and antinuclear antibodies (ANAs) are the most common autoimmune antibodies, accounting for 55%.[1] However, we found only 1/8 patient with ANA positive. This is an interesting phenomenon, considering a bias may be introduced due to a small sample size in our study, we need more studies to confirm whether there is a difference between Chinese and Western in autoantibodies.

Four patients presented hearing loss, this is beyond previous literature reports. One of them was due to frequentative auditory tube infection, the other three without definitive cause. Whether there is a relationship between hearing loss and GS is unknown, doctors could pay attention to this aspect to confirm it in the future.

Thus far, GS has no definitive therapeutic schedule, but thymectomy and immunoglobulin replacement treatment have become the most important management approach. Thymectomy has a positive effect on myasthenia gravis and PRCA, although it has no effect on immunological

abnormalities.[37,46] In one case, thymectomy might have worsened the hypogammaglobulinemia.[47] Immunoglobulin replacement treatment has been reported to play a favorable role in controlling infection. A retrospective review reported that 23 of 30 patients had a reduction of bacterial sinopulmonary infections after receiving immunoglobulin treatment.[39] Intravenous immunoglobulin (IVIG) was superior to intramuscular immunoglobulin replacement (response rate of 88% vs. 62%).[37,39]

Common variable immune deficiency (CVID) is one of the most common symptomatic primary immunodeficiency syndromes in China, which is also characterized by hypogammaglobulinemia and recurrent infections.[48] However, in contrast to CVID, which typically occur in the pediatric population, GS has a poorer prognosis with a high mortality of approximately 45–57%, with infection being the most common cause of death.[1,39,49] In a single-center review of primary antibody deficiency spanning 20 years, 70% of patients with GS were alive 5 years after the onset of symptoms, compared with almost 100% of patients with CVID. At 10 years, only 33% were alive, compared with 95% of patients with CVID.[50] Other causes contributing to death are an autoimmune disease and hematological complications.[37] The prognosis is mainly determined by the severity of associated infectious, hematologic, and autoimmune diseases, rather than by the behavior of the thymoma.[51]

There are some limitations to this systematic review. First, the amount of included studies is small. Second, the studies included were case reports or case studies, which might decrease the quality of evidence, more studies of high quality are required to unravel the mystery of GS.

In conclusion, GS is a rare association of thymoma and immunodeficiency with a poor prognosis. The initial clinical presentation is varied, ranging from symptoms related to the thymoma to infections resulting from immunodeficiency. Gastrointestinal and autoimmune manifestations are common complications. With respect to treatment, thymectomy and IVIG are the primary GS therapies. Astute clinical acumen and increased awareness regarding the clinical and immunological profile of this syndrome might increase the early recognition of this syndrome and decrease the mortality.

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Conflicts of interest

There are no conflicts of interest.

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