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Understanding the uncommon: Insights into thymoma associated immunodeficiency

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Abstract

Background: Thymoma-associated immunodeficiency (TAI) is a rare, acquired adult-onset immunodeficiency. It includes the classic form of Good syndrome (GS), characterized by thymoma and hypogammaglobulinemia, as well as a non-classic form of GS. This condition leads to specific or combined deficiencies in both B- and T-cells, causing considerable morbidity and mortality, although the underlying immunopathology is still not well understood.

Objective: In this study, we examine the clinical features, laboratory investigations, immunological analysis and treatment outcomes of 21 patients with TAI in our institution, and its associated comorbidities and complications.

Methods: Patients with thymoma and recurrent infections who were followed up in our immunodeficiency clinic between 1 January 1999 and 1 December 2023 were identified. Clinical information, laboratory, treatment and outcome data were extracted from the medical records. Seven patients agreed to provide additional blood samples for anti-cytokine antibodies profiling.

Results: Of the 21 TAI patients, 12 (57.1%) were females and the mean age at diagnosis of TAI was 61.3 ± 9.2 years. 19 patients had classic GS. 12 (57.1%) had underlying bronchiectasis, 5 (23.8%) had sinusitis and 5 (23.8%) developed malignancy other than thymic carcinoma after diagnosis of thymoma. 10 patients (47.6%) developed autoimmune conditions including myasthenia gravis, polymyositis, lichen planus, vasculitis and ulcerative colitis. One patient was found to have high titre of neutralizing anti-interferon alpha antibodies as well as medium titre of neutralizing anti-interleukin 17 antibodies. 9 patients died at a median of 4.2 (IQR 1.98 – 4.9) years after diagnosis of TAI.

Conclusion: TAI is associated with significant morbidity and mortality. The syndrome leads to a plethora of opportunistic infections, autoimmune complications and malignancy.

Key words: thymoma, immunodeficiency, Good syndrome, hypogammaglobulinemia, anti-cytokine antibody

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Introduction

Good syndrome (GS) was first described by Dr Robert Good in 1954, the eponymous physician who noted an association between thymoma and hypogammaglobulinemia. There is no established international diagnostic criteria for GS. It was initially classified as a subset of common variable immunodeficiency (CVID).[1] However, this classification is debatable, as CVID is usually a condition with impaired B-cell maturation, whereas GS is associated with low peripheral B cells number. Subsequently, it was classified as a distinct entity under phenocopies of inborn errors of immunity in the 2022 International Union of Immunological Societies update.[2]

Recently, a new clinical spectrum of thymoma associated immunodeficiency (TAI) was proposed to capture cases of classic GS and non-classic GS.[3] Classic GS comprise of patients with thymoma and hypogammaglobulinemia. In contrast, non-classic GS comprise of patients with either normal levels of serum immunoglobulins (Ig) but having severely low $CD4^+$ T cell levels, presence of autoantibodies to cytokines or normal IgG but low IgA and IgM and other miscellaneous cases.

Individuals with TAI often experience recurrent infections, particularly of the respiratory tract, due to hypogammaglobulinemia. The rarity of TAI poses a significant diagnostic dilemma, often requiring a high index of suspicion, comprehensive immunological evaluation, and imaging studies to confirm the presence of thymoma. TAI remains relatively poorly defined and likely underdiagnosed. This could have led to significant morbidity and mortality to patients who likely had the disease but did not receive timely and appropriate treatment for their condition.

In this study we aim to review the clinical features, laboratory values, immunological evaluation and treatment outcomes of TAI patients followed up in a tertiary adult institution in Singapore spanning over a 24-year duration.

Methods and Materials

Patients with a medical history of thymoma and hypogammaglobulinemia, or thymoma with recurrent infections were included in this study.

A total of 21 patients were diagnosed with TAI in Tan Tock Seng Hospital, Singapore between 1 January 1999 and 1 December 2023. A chart review was performed for these patients. Key information on past medical history, the first radiological report of thymoma, immunologic workup, treatment received, infections and autoimmune conditions were collected. The study was approved by the institutional review board (National Healthcare Group, Domain Specific Review Board DSRB reference number 2022/00211) for waiver of consent for retrospective data collection. A subsequent approval was obtained from our institution review board (DSRB reference number 2022/00052) and written informed consent was obtained from 7 individuals for collection of their blood samples for sampling of anti-cytokine antibodies analysis.

Enzyme Linked Immunosorbent Assay (ELISA) for the detection of anti-interferon gamma (anti-IFNγ,) anti-IFN alpha (anti-IFNα) and other anti-cytokine autoantibodies

For the detection of anti-cytokine antibodies (ACAA) in our cohorts, 96-well microplates (Nunu Maxisopt, Demark) were pre-coated each with a specific anti-cytokine antibody assayed by commercial ELISAs according to the manufacturers' recommendations (BD Pharmingen or ThermoFisher). Briefly, microplates were precoated with 50 µl of anti-human IFNγ or anti-human IFNα in 0.1 M NaH_2CO_3 (Sigma-Aldrich, St Louise, MO) overnight at 4°C. The plates were washed 3 times in phosphate buffer (PBS)-0.05% Tween 20 (PBST, Sigma) and blocked in PBS-10% fetal bovium serum (PBS/10% FBS, from here refer as assay buffer, Gibco) for 1 hour at room temperature (RT). Separately, serum from patients and donors were serially diluted (10^{-2} to 10^{-6}) and incubated with assay buffer spiked with either 200 pg/ml of recombinant IFNγ or 100 pg/ml of recombinant IFNα (both from e-Bioscience) in a shaking incubator for 1 hour RT. After blocking, the precoated cytokine plates were washed and a mixture of recombinant IFNγ or recombinant IFNα as standards, together with diluted serum samples were added for 2 hrs of incubation, followed by incubation with specific detection antibody and developed with tetramethylbenzidine substrate (Sigma-Aldrich). In the neutralising assays, the blocking index was defined as the maximum dilution from (10^{-2} to 10^{-6}), with inhibiting index defined at 50% of either 200 pg/ml of IFNγ or 100 pg/m of IFNα measurement. Similar technique was employed to assay for anti-interleukin (IL)12(p40), anti-IL12(p70), eBioscience, San Diego, USA) or anti-IL-17 (R&D systems) when clinic needs arise. In addition, human anti-IFNα was quantified using an ELISA kit directly coated with recombinant human IFN-α. Levels in serum samples were detected according to the manufacturer's instructions with secondary conjugate antibodies (BMS217, Invitrogen, ThermoFisher), with lowest detection limit of 3.1 ng/ml and > 120 ng/ml considered to be positive,[4] prior to proceeding with subsequent neutralisation and flowcytometry study.

Statistical method

Patient characteristics were summarised using descriptive analyses. All statistical analyses were performed using the Intercooled STATA (Stata Corporation, College Station, USA).

Results

Demographics

Of the 21 TAI patients, 12 (57.1%) were females and 9 (42.9%) were male. There were 18 (85.7%) Chinese and 3 (14.3%) Malay patients. The mean age at diagnosis was 61.3 ± 9.2 years and mean follow-up duration was 6.4 ± 6.0 years. **Table 1** summarizes all demographic and clinical characteristics of the patients.

Diagnosis and classification

Of the 21 patients, 19 (90.5%) had classic GS. A total of 8 patients (38.1%) were concurrently diagnosed with thymoma and immunodeficiency, 13 (61.9%) were diagnosed with TAI on average 7.8 ± 4.1 years after diagnosis of thymoma. 18 (85.7%) patients underwent thymectomy and 7 (33.3%) had adjuvant radiotherapy. Of the 18 patients who underwent thymectomy, the most common predominant World Health Organisation (WHO) histologic subtype was AB (5).[5] Other subtypes include A (2), B2 (1), B3 (1) and C (1). Three had mixed subtype of B2/B3 and 2 had mixed subtype of A/B1/B2 while 3 had no recorded histologic subtype.

Table 1. Demographic and clinical characteristics of TAI subjects.

	Gender	Age at diagnosis of TAI (years)	Age of thymoma diagnosis	Infections; complications	Organisms	Autoimmunity (if Yes, state the condition)	Malignancy	Thymoma WHO subtype	Treatment			Death	Survival (years from diagnosis)
									Thymectomy	Radiotherapy	IVIg		
Summary	**F: 12 (57.1%) M: 9 (42.9%)**	**Mean (SD): 61.3 ± 9.2**	**Mean (SD): 56.5 ± 10.5**	**RTI: 20 (95.2%) GI: 9 (42.9%) OI: 3 (14.3%) BC: 12 (57.1%) SS: 5 (23.8%)**	**Bacteria: 14 (66.7%) CMV: 5 (23.8%) Mycobacteria: 4 (19.0%) Candidiasis: 5 (23.8%) Severe COVID-19: 3 (14.3%)**	**10 (47.6%)**	**5 (23.8%) *other than thymic carcinoma**	**AB: 5 A: 2 B2: 1 B3: 1 C: 1 Mixed: 5 Unknown: 3**	**18 (85.5%)**	**7 (33.3%)**	**14 (66.7%)**	**9 (42.9%)**	**Median (IQR): 4.4 (4.5)**
1	M	54	41	RTI, GI, OI; SS	CMV, Campylobacter, M. abscesses, Candida	No	Colorectal adenocarcinoma	unknown	Yes	No	Yes	Yes	11.6
2	F	69	54	RTI, GI; SS, BC	*Streptococcus pneumoniae*, *Strongyloides stercoralis*	No	No	B2, B3	Yes	No	No	Yes	4.4
3	M	64	64	GI	Salmonella, Candida	No	Metastatic thymoma	C	Yes	No	Yes	Yes	4.4
4	M	67	67	RTI, GI; BC	MRSA, Candida	No	No	N.A.	No	No	Yes	Yes	4.9
5	M	69	62	RTI, GI; SS, BC	*Streptococcus pneumoniae*, *Haemophilus influenzae*	Ulcerative colitis	No	AB	Yes	No	Yes	Yes	2.6
6	F	66	63	RTI, OI	CMV	Cryptogenic organising pneumonia	No	unknown	Yes	No	Yes	Yes	4.2
7	F	43	43	RTI; SS	N.A.	Oral lichen planus	No	A	Yes	No	No	No	11.0
8	F	62	55	RTI; BC	M. abscesses	No	No	AB	Yes	No	No	No	2.78
9	F	75	75	RTI; BC	SARS-CoV2	No	No	N.A.	No	No	No	Yes	1.98
10	F	40	33	RTI	M. gordonae, *Haemophilus influenzae*	Myasthenia gravis	Breast carcinoma	B2	Yes	Yes	Yes	No	7.07
11	F	54	54	RTI	Candida	Polymyositis	No	B2, B3	Yes	No	Yes	Yes	6.7
12	M	57	44	RTI	N.A.	Myasthenia gravis & alopecia areata	No	B2, B3	Yes	Yes	No	No	7.07

Table 1. (Continued)

	Gender	Age at diagnosis of TAI (years)	Age of thymoma diagnosis	Infections; complications	Organisms	Autoimmunity (if Yes, state the condition)	Malignancy	Thymoma WHO subtype	Treatment			Death	Survival (years from diagnosis)
									Thymectomy	Radiotherapy	IVIg		
Summary	**F: 12 (57.1%) M: 9 (42.9%)**	**Mean (SD): 61.3 ± 9.2**	**Mean (SD): 56.5 ± 10.5**	**RTI: 20 (95.2%) GI: 9 (42.9%) OI: 3 (14.3%) BC: 12 (57.1%) SS: 5 (23.8%)**	**Bacteria: 14 (66.7%) CMV: 5 (23.8%) Mycobacteria: 4 (19.0%) Candidiasis: 5 (23.8%) Severe COVID-19: 3 (14.3%)**	**10 (47.6%)**	**5 (23.8%) *other than thymic carcinoma**	**AB: 5 A: 2 B2: 1 B3: 1 C: 1 Mixed: 5 Unknown: 3**	**18 (85.5%)**	**7 (33.3%)**	**14 (66.7%)**	**9 (42.9%)**	**Median (IQR): 4.4 (4.5)**
13	F	72	71	RTI, GI; BC	CMV, Aspergillosis, *Proteus mirabilis*, *Providencia rettgeri* SARS-CoV-2	No	Bladder carcinoma, scalp basal cell carcinoma	A, B1, B2	Yes	Yes	Yes	Yes	1.77
14	M	61	59	RTI; BC	E. coli, *Enterobacter aerogenes*, Rhinovirus	Myasthenia gravis	No	B3	Yes	Yes	Yes	No	2.69
15	F	57	50	RTI; BC	*Pseudomonas aeruginosa*	Myasthenia gravis & cryptogenic organising pneumonia	No	A, B1, B2	Yes	Yes	No	No	0.98
16	M	60	60	RTI	N.A.	Myasthenia gravis	Colorectal adenocarcinoma	Unknown	Yes	No	No	No	0.95
17	F	61	50	RTI, GI; SS	*Haemophilus influenza*	No	No	AB	Yes	No	Yes	No	27.2
18	M	63	63	RTI, GI; BC	Campylobacter	No	No	AB	Yes	No	Yes	No	11.8
19	F	55	48	RTI; BC	*Streptococcus pneumoniae*, *Haemophilus influenzae*	Vasculitis	No	AB	Yes	Yes	Yes	No	10.7
20	M	76	68	RTI; BC	Fusobacterium, CMV, SARS-CoV-2, *Stenotrophomonas maltophilia*	No	No	N.A.	No, patient declined	No	Yes	No	1.6
21	F	62	62	RTI, GI, OI; BC	CMV, M. abscesses, Salmonella, Fusarium, Candida	No	Hepatocellular carcinoma	A	Yes	Yes	Yes	No	7.0

BC; Bronchiectasis, CMV; cytomegalovirus, E. coli; Escherichia coli, F; Female, GI; Gastrointestinal infections, M; Male, M. abscesses; Mycobacterium abscesses, M. gordonae; Mycobacterium gordonae, MRSA; Methicillin resistant staphylococcus, OI; Ocular infections, RTI; Respiratory tract infections, SARS-CoV-2; severe acute respiratory syndrome coronavirus 2, SS; Sinusitis, WHO; World Health Organisation

Table 2. Immunological and Laboratory features of TAI Subjects.

	IgG (7.0–18 g/L)	IgA (1.2–4.4 g/L)	IgM < 4.5 (0.4–2.4g/L)	Lymphocyte (× 10^9/l)	CD4 (cells/ uL)	Low CD19 (< 5 cells/uL)	Antibody response to pneumococcal vaccine	Antibody response to tetanus vaccine	Anti-IFNα (ng/ml)	Anti-IFNα Neutralising ELISA	Anti-IFNγ	Anti IL17
1	3.27	0.44	0.1	1.63	393	N	Reduced	Reduced	N.A.	N.A.	N.A.	N.A.
2	3.9	0.25	0.2	1.53	187	Y	Reduced	Reduced	N.A.	N.A.	N.A.	N.A.
3	2.8	< 0.25	< 0.2	1.22	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
4	< 2.0	<0.4	< 0.3	0.98	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
5	< 2.0	< 0.4	< 0.3	1.45	N.A.	N.A.	Reduced	N.A.	N.A.	N.A.	N.A.	N.A.
6	5.9	0.4	< 0.3	0.83	415	Y	Reduced	Normal	N.A.	N.A.	N.A.	N.A.
7	6.5	1.3	0.4	1.43	N.A.	N.A.	Reduced	Normal	N.A.	N.A.	N.A.	N.A.
8	3.6	< 0.4	0.4	0.82	205	Y	Reduced	N.A.	N.A.	N.A.	N.A.	N.A.
9	< 2.0	< 0.4	< 0.3	3.6	N.A.	N.A.	Reduced	Normal	N.A.	N.A.	N.A.	N.A.
10	3.7	0.8	0.6	4.31	N.A.	N.A.	Reduced	Normal	N.A.	N.A.	N.A.	N.A.
11	5.1	1.1	< 0.3	1.16	N.A.	Y	Reduced	Reduced	N.A.	N.A.	N.A.	N.A.
12	6.8	1.1	2.3	0.40	N.A.	N.A.	Reduced	Normal	N.A.	N.A.	N.A.	N.A.
13	< 2.0	< 0.4	< 0.3	1.63	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
14	9.9	0.8	< 0.3	0.69	< 20	N.A.	Reduced	N.A.	N.A.	N.A.	N.A.	N.A.
15	11.6	1.7	1.0	1.15	318	N	N.A.	N.A.	12592.3	1/68,000*	Negative	Positive
16	6.4	1.9	0.7	1.24	N.A.	Y	Reduced	Normal	20.5	Negative	Negative	Negative
17	1.84	0.15	0.16	0.68	88.4	N	Reduced	Reduced	20.1	Negative	Negative	Negative
18	2.29	0.19	< 0.04	2.20	506	Y	Reduced	Reduced	305.9	Negative	Negative	Negative
19	< 2.0	< 0.4	< 0.3	2.48	447	N	Reduced	N.A.	93.3	Negative	Negative	Negative
20	2.3	0.4	< 0.3	1.98	N.A.	Y	N.A.	N.A.	4.8	Negative	Negative	Negative
21	6.6	< 0.4	< 0.3	1.95	487	N	Reduced	Reduced	41.9	Negative	Negative	Negative

*Inhibition in IFNα induced STAT-1 phosphorylation, with neutralising level achieved N/10
N.A.; Not available, ELISA; Enzyme Linked Immunosorbent Assay

Immunological abnormalities included low IgG (< 7 g/L), low IgA (< 0.8 g/L) and low IgM (< 0.3 g/L) in 19, 14 and 15 patients respectively. 7 (33.3%) had a $CD19^+$ B cell level of < 5 cells/ul (**Table 2**). 16 (76.2%) had inadequate response to capsular polysaccharide (Pneumovax23®) vaccination and 6 (28.6%) to tetanus toxoid vaccination. Of the 2 patients with non-classic GS, 1 had $CD4^+$ T cell levels < 20 cells (subject 14) and the other had high titre neutralizing anti-IFNα and medium titre neutralizing IL-17 antibodies (subject 15).

7 patients were screened for anti-cytokine antibodies (**Table 2**). Two had raised anti-IFNα titres (305 and 12,592 ng/ml), however only one patient had demonstrated cytokine neutralising assay with half maximal inhibitory concentration (IC_{50}) at 68,000 and inhibition of Signal Transducer and Activation of Transcription 1 (STAT-1) phosphorylation by flowcytometry. The same patient was also found to have raised anti-IL-17 antibodies with cytokine neutralising assay IC_{50} at 3,200. The patient (subject 15) with neutralizing levels of anti-IFNα and anti-IL-17 antibodies is a 57-year-old female patient with history of stage IIa type B1 thymoma, myasthenia gravis, cryptogenic organizing pneumonia and bronchiectasis. She has recurrent respiratory tract infections including previous *Pseudomonas aeruginosa* respiratory infection as well as recurrent oral candidiasis and onychomycosis. Her total serum IgG is unremarkable (11.6g/L, lab reference range 7-18g/L) and without T cell lymphopenia. We postulate the neutralising levels of anti-IFNα and anti-IL-17 antibodies may contribute to immune dysregulation within her T cell compartment and result in her recurrent infections. It would be of interest to evaluate her qualitative B cell function, however the patient has declined both pneumococcal and tetanus vaccine stimulation testing. She is currently treated with intensive chest physiotherapy and intermittent antibiotic prophylaxis.

Finally, 17 out of the 21 patients were recommended monthly intravenous immunoglobulin (IVIG) replacement at 400mg/kg body weight. 4 patients with mildly reduced IgG levels (> 6 g/L, lab reference range 7-18 g/L) without recurrent infections were deemed not to require IVIG replacement and were put on 4-6 monthly monitoring of IgG levels and frequency/ severity of infections. Of the 17 patients, only 14 received monthly IVIG as 3 patients refused treatment.

Morbidity and Mortality

The infections reported in all patients include: 14 (66.7%) bacteria, 5 (23.8%) cytomegalovirus (CMV), 4 (19.0%) mycobacteria or non-tuberculous mycobacterium, 5 (23.8%) non-invasive candidiasis and 3 (14.3%) severe coronavirus 2019 (COVID-19) infection (**Table 1**).

Three patients suffered severe COVID-19 infection requiring intensive care support despite receiving at least 2 doses of Pfizer-BioNTech/Comirnaty COVID-19 vaccination, with an average length of hospitalisation stay of 89 days (range 58-107). Two patients failed to exhibit antibody seroconversion after 2 doses of Pfizer-BioNTech/Comirnaty COVID-19 vaccination (Roche Elecsys SARS-COV-2 Spike antibody: non-reactive). Two patients with severe COVID-19 were newly diagnosed with GS, as the severity of COVID-19 and presence of thymoma prompted physicians to check their immunoglobulin levels. One patient was on regular monthly IVIG replacement and had a trough IgG level of 6.2g/L prior to contracting COVID-19 infection.

Over half of all GS patients (12 (57.1%)) were diagnosed with bronchiectasis, while 5 (23.8%) had sinusitis and 4 (19.0%) developed malignancy other than thymic carcinoma after diagnosis of thymoma.

Ten patients (47.6%) developed autoimmune conditions including myasthenia gravis, polymyositis, lichen planus, vasculitis and ulcerative colitis. These patients required immunosuppressants including combination prednisolone and methotrexate, azathioprine or mycophenolate mofetil. Replacement IVIG was continued in 6 of these patients, with none requiring immunomodulatory dose of 2 g/kg IVIG to treat the underlying autoimmune condition.

Nine patients died at a median of 4.2 (IQR 1.98–4.9) years after diagnosis of TAI. 5 patients with underlying bronchiectasis succumbed to pneumonia, and 1 died from severe COVID-19 pneumonia. One died from colorectal cancer, and 1 patient died from metastatic thymic carcinoma. The last patient had no recorded cause of death.

Brief Review

The disease

TAI is rare and our cohort represents one of the largest case series in Asian patients.[6,7] The typical journey of a TAI patient is depicted in **Figure 1**. In our cohort, majority of the patients were diagnosed between the sixth to eighth decade of life. The age at which our patients are diagnosed with TAI is comparable to other cohorts; a systematic review of 162 GS patients found the median age at diagnosis to be 58 years.[8] Most patients were diagnosed with classic GS years after diagnosis of thymoma, with hypogammaglobulinemia detected a significant period after the patient had a known thymoma, the shortest being 1 year and longest being 15 years. Theodoros et al. found that in 56 (42.4%) of 132 patients, the diagnosis of thymoma precede the diagnosis of hypogammaglobulinemia, infection, or diarrhoea, with intervals ranging from 3 months to 18 years.[9]

TAI patients have increased susceptibility for bacterial, viral and fungal infections, and tend to be associated with autoimmune diseases and malignancies.[10] The prevalence of autoimmunity and malignancies in GS patients varies between 25-76% and 1-6% respectively across different cohorts.[8]

42.9% of our patients demised at a median of 4.2 years after diagnosis, with most succumbing to infectious complications of the disease, while some demised from cancer-related deaths. Severe COVID-19 infections also contributed to significant morbidity to 3 GS patients who required ICU admissions contributing to prolonged hospitalisation, and 1 ultimately succumbed from the condition. Prognosis of GS patients are reported to be poorer compared to other immunodeficiencies. In a single-center review of primary antibody deficiency conducted over 20 years, 5-year survival was 70% for GS patients compared to nearly 100% of those

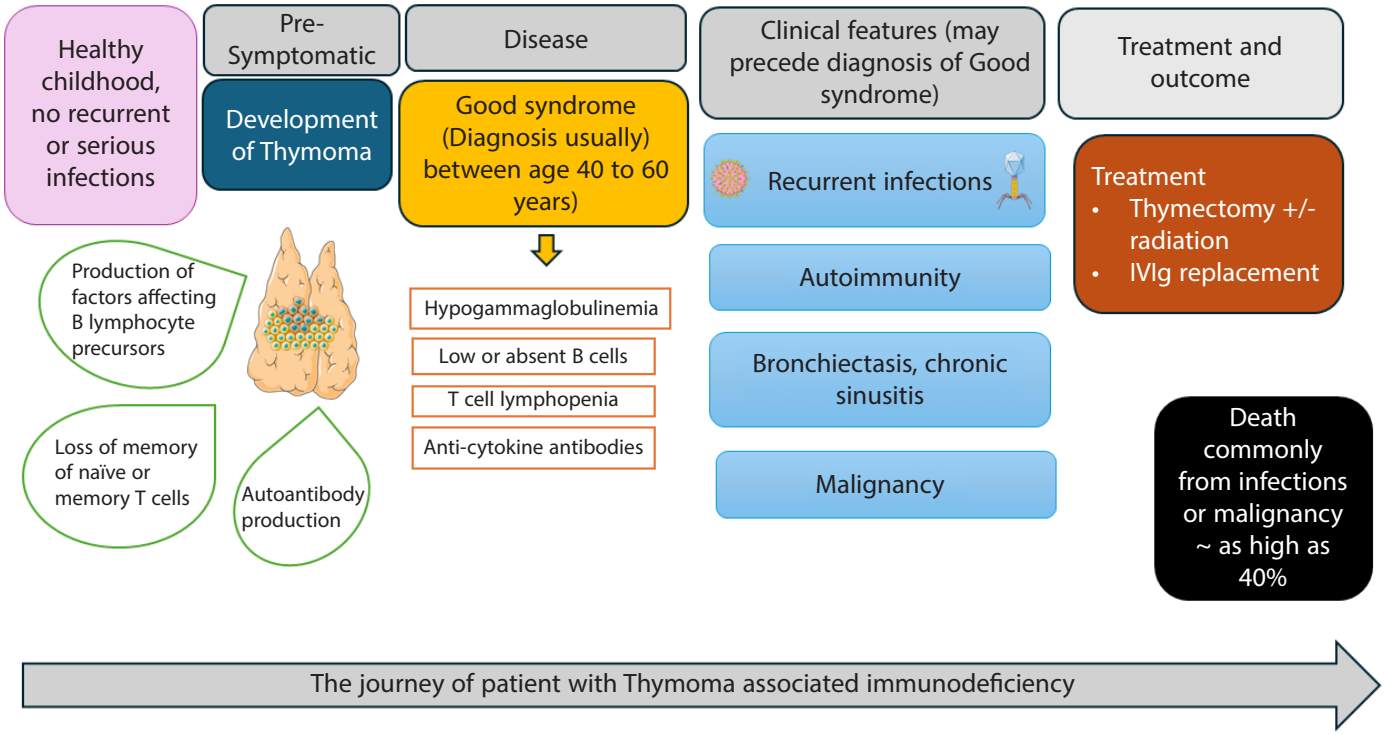

Figure 1.

with common variable immunodeficiency (CVID).[11] 10-year survival was only 33% for GS patients compared to 95% for CVID patients. A systematic review of 152 cases of Good's syndrome revealed a significant overall mortality rate of 46%.[9]

A limitation of our study is that histology was only available for 15 of the 18 patients who underwent thymectomy. The histological report was not available as thymectomy was carried out in a different institution for 3 patients and the report was not provided to the managing immunologist. Similar to other cohorts, the most common histological subtype was that of AB.[12]

Pathophysiology

There are various proposed mechanisms which result in humoral and cell-mediated immunodeficiency observed in TAI, as we attempt to summarise below.

The first mechanism is through cytokines such as limitin, an IFN-like cytokine produced by bone stromal cells, which influence B cell precursors. It is suggested that these cytokines could preferentially inhibit B cell growth, maturation and plasma cell differentiation.[13]

The second mechanism involves the thymoma and its association with autoantibodies. This purports that TAI takes on a similar pathophysiology to other paraneoplastic phenomena associated with thymoma such as pure red cell aplasia (PRCA). In PRCA, T cells and autoantibodies are shown to be able to directly or indirectly inhibit erythropoiesis.[14] In other studies, T cells from patients with thymoma were shown to be able to inhibit pre-B cell growth[15] and immunoglobulin production from B cells.[16]

Various anti-cytokine antibodies have been reported in patients with thymic neoplasia. Functional testing has shown that these autoantibodies directed against IFNα, IFNβ, IL-1α, IL-12p35, IL-12p40, and IL-17A had neutralising biologic blocking activity *in vitro*.[17] A case report described a patient with thymoma and hypogammaglobulinemia, recurrent infections, high titre antibodies against IFNα and low titre antibodies to granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-6.[18] Consistent with previous studies, we found high antibody titres to IFNα and medium antibody titres of IL-17 in one patient. Anti-cytokine antibodies are not routinely available commercially and often remain used in research settings. With increasing discovery of autoantibodies to cytokines, it may be beneficial to search for autoantibodies to cytokines in patients with mild hypogammaglobulinemia who experience autoimmunity, recurrent or opportunistic infections. There may be a potential for early treatment and suppression of anti-cytokine antibodies in altering the disease course in these patients with TAI.

The third mechanism is based on the observation that the opportunistic infections seen in GS are associated with a defect in cell-mediated immunity. This would imply that there is a loss in either the naive or long term memory $CD4^+$ T cells. *In vitro* studies performed in patients with GS have shown reduction in T lymphocyte proliferation and IL-2 production, resulting in severe $CD4^+$ lymphopenia.[19] Detailed immunophenotyping of a cohort of 9 GS patients found reduced circulating $CD4^+$ T cells, NK cells, basophils and neutrophils.[20]

In our cohort, 2 patients did not exhibit hypogammaglobulinemia (Subject 15 and 19) and yet experienced recurrent serious infections. Subject 15 was found to have elevated anti IFNα antibodies that are neutralizing as well as anti-IL-17 antibodies. Subject 19 has extremely low < 20 cells/uL $CD4^+$ T cell levels. These cases illustrate additional mechanisms beside hypogammaglobulinemia may contribute to infections in these patients.

Management

The management of GS are broadly divided into management of the immunological abnormalities and the thymoma.

Intravenous immunoglobulin (IVIG) replacement remains the mainstay of treatment of the hypogammaglobulinemia observed in GS. A retrospective study of patients who received IVIG in the treatment of GS demonstrated that 23 of 30 patients had a reduction in the number of bacterial sinopulmonary infections.[21] Three of the patients in our cohort who refuse IVIG replacement experienced recurrent infections. Two demised from infections 1.98 and 4.4 years after being diagnosed with GS.

Surgical intervention is the first-line of management for the thymoma. While thymomas are generally considered slow-growing tumours, there is always a potential for local invasive growth and malignancy. Furthermore, the most important prognosis for patients with thymoma is the completeness of tumour resection.[22] In stage 3 or 4 disease, patients with thymoma may also be offered radiotherapy and combined chemotherapy.

Unfortunately, unlike in myasthenia gravis, there is little evidence to suggest that thymectomy reverses the immunological abnormalities seen in GS.[23] This would further strengthen the hypothesis that the hypogammaglobulinemia seen in GS is an association rather than the result of the thymoma, and that the depletion of B cells could be due to the B cell-inhibiting cytokines produced in the bone marrow.

Early detection of TAI

Regrettably, many patients with thymoma are only recognised to have GS many years later, after infectious or autoimmune complications prompt immunological investigations which unravels the patient's hypogammaglobulinemia. One such patient in our cohort diagnosed with a thymoma was only formally diagnosed with GS 15 years later. Within this period, the patient could have received IVIG which could have prevented the morbidity of a plethora of infections.

There is evidence to support routine measurement of serum immunoglobulin levels upon first diagnosis of a thymoma. One study showed that the incidence of hypogammaglobulinemia in patients with thymoma is 6-11%.[24] Kelleher P et al suggest trending immunoglobulin every other year, because of cases in which progressive immunodeficiency have been observed.[25] Furthermore, computed tomographic (CT) imaging can be considered on first diagnosis of an anterior mediastinal mass on chest X-ray, as it can not only evaluate the thymoma itself but also look for associated respiratory complications of GS such as bronchiectasis or pulmonary tuberculosis. A CT thorax should also be routinely offered to patients with clinical suspicion of a thymoma even if not seen on chest X-ray, as a study showed that up to 25% of thymomas were missed on a chest X-ray, resulting in an average diagnostic delay of 41 months.[26]

Conclusion

While rare and not fully understood, TAI is undoubtedly linked with significant morbidity and mortality that warrant our attention and further study. These include opportunistic infections, autoimmune complications and malignancy, which in many instances lead to the patient's demise.

Further studies is essential to elucidate the possible mechanisms underlying the disease, and improve treatment modalities. Current therapies aim at "repairing" the damage caused by TAI through IVIG replacement, rather than addressing the root cause. Unlike myasthenia gravis which can be significantly reversed through a thymectomy, this approach has limited efficacy for preventing TAI-related complications. Research into the current theories of GS could lead to development of novel targeted therapies which can help prevent B cell inhibition, and reverse $CD4^+$ lymphopenia.

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