Myasthenia gravis associated with Good's syndrome: a case report and review of literature

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Abstract

Background: Good's syndrome (GS) is a rare secondary immunodeficiency disease associated with thymoma, which is characterized by chronic recurrent infection. Due to abnormal immune function, more than half of GS are complicated with autoimmune diseases, such as myasthenia gravis (MG) and pure red cell aplastic anemia (PRCA).

Case presentation: We report a case of type III late-onset myasthenia gravis (MG) with thymoma, which was gradually improved after mechanical ventilation, Intravenous steroid pulse, intravenous immunoglobulin , and tacrolimus. After weaning, the patient had a repeated myasthenia gravis crisis caused by lung infections, urinary tract infections, bacteremia, and septic shock, resulting in difficulty in weaning. The subsequent immunological evaluation showed hypogammaglobulinemia, decreased B lymphocytes , and an inverted proportion of CT4+/CD8+ cells, which confirmed the diagnosis of GS.

Conclusions: GS should be strongly suspected and immunological examinations performed when recurrent opportunistic infections occur in patients with MG associated thymoma. Early identification and intravenous administration of immunoglobulin can reduce the incidence of future infection and improve the prognosis. As the disease is rare, misdiagnosis and missed diagnosis are common to happen. it is important for neurologists to recognize the clinical characteristics of MG patients with GS. We summarize 16 previously reported cases of MG patients with GS. The average age of onset of MG was 53 ±18 years old, and the ratio of male to female was roughly equal. Mostly manifested as systemic myasthenia gravis (77%), half of the patients had bulbar paralysis, 15% had myasthenia gravis crisis, and only 8% only involved extraocular muscles. Thymomas of type B and Type A were the most common. GS symptoms improved in 7 of the 10 patients who underwent thymectomy, which suggested that thymectomy played a positive role in its treatment.

Keywords: Good's syndrome, thymoma, myasthenia gravis, immunodeficiency

1. Introduction

The thymus is the site of T lymphocytes differentiation and maturation. Thymoma is a rare thymic epithelial tumor and the most common mediastinal tumor in adults. 27% ~ 59% of thymoma patients have paraneoplastic autoimmune diseases, the most common is MG, and 15% ~ 20% of thymoma patients have MG [Error: Reference source not foundError: Reference source not found]. However, more than 80% of MG patients have abnormal thymus, 65% have thymic hyperplasia, and 10% ~ 20% have thymoma.

GS, also known as thymoma with immunodeficiency(TWI), is a rare adult-onset thymoma-related humoral and cellular immunodeficiency disease. It was first described and reported by RobertGood in 1954. GS tends to occur in adults aged 40 to 70, women are slightly higher than men, accounting for 5% of thymoma patients[Error: Reference source not found]. 58.6% ~ 76% of GS patients have secondary autoimmune diseases[Error: Reference source not foundError: Reference source not found].

The most common is PRCA, approximately 34.8% of patients have PRCA[Error: Reference source not foundError: Reference source not found]. MG is the second most common autoimmune complication of GS. 9.1 % ~ 15.7 % of GS patients suffer from MG[Error: Reference source not foundError: Reference source not found]. It's immunological manifestations are as follows: Peripheral blood B cell decrease or absence, NK cell decrease, T lymphocyte proliferation response to mitogen stimulation, CD+4 lymphocyte decrease, CD+8 lymphocyte increase, CD+4/CD+8T cell proportion inversion, and hypogammaglobulinemia, etc. GS is characterized by thymoma, hypogammaglobulinemia, and immunodeficiency. Hypogammaglobulinemia is not necessarily present. Thymoma with infectious susceptibility is called GS in a broad sense. Reports of MG complicated with broad sense GS can be seen everywhere, while GS complicated with hypogammaglobulinemia (narrowly defined) is extremely rare. Only 16 cases （8, 9 ~ 22）were found in the literature (Table 1). Here we report a case of MG with GS and summarize the previously reported cases.

2. Case presentation

We report a 57-year-old woman who was treated in our hospital in October 2019 because of "vague speech, dysphagia for 2 months, aggravation with limb weakness for half a month".The results of the neostigmine test were positive. repetitive nerve stimulation showed that RNS decreased in low frequency (bilateral facial nerve and left accessory nerve). Chest CT showed the presence of a thymoma. And was diagnosed with MG and thymoma. After oral prednisolone (60 mg once a day) and brombitamine, the symptoms gradually improved. and the dose of prednisolone was gradually reduced after the condition was stable. The patient refused to undergo the thymectomy. In February 2020, the patient experienced dysphagia again due to overwork and failure to take brombitamine on time, accompanied by progressive neck lifting weakness and limb weakness, and a few days later, she developed dyspnea. Blood gas analysis showed hypoxemia, she was diagnosed with myasthenia gravis crisis, endotracheal intubation, and ventilator were given to assist breathing. Admission physical examination: endotracheal intubation, ventilator-assisted breathing, a clear mind, bilateral pupils with the equal circle, about 3mm in diameter, sensitive to light reflex, isotropic movement of both eyes, cervical flexor muscle strength grade 2, limb muscle strength grade 4, moderate muscle tension, limb tendon reflex (+), double Babbitt sign (-).

Laboratory examination: Re-examination of chest CT showed that the volume of thymoma was smaller than before. Neuromuscular disease spectrum showed anti-AChR antibody IgG (+), anti-skeletal muscle antibody IgG (+), anti-myocardial antibody IgG (+), anti-Titin antibody IgG (+). Blood cell analysis (2020-9-30): white blood cells 20.4×10^{9} /L, red blood cell 1.96×10^{12} /L, hemoglobin 61 g/L, mean red blood cell volume 96.4 fL, average red blood cell hemoglobin 31.1 pg, Mean red blood cell hemoglobin concentration 323g/L, lymphocyte percentage 4.5%, neutrophil percentage 92.8%. Bone marrow flow cytometry examination (2020-9-30): mature lymphocyte group 6.46%, myeloid primordial cell group 0.21%, mature granulocyte group of immature muscle 86.23%, mature monocyte group 0.73%, immature red blood cell group 3.84%, acid phagocyte group 1.03%. Complement + immunoglobulin (2020-9): complement C1q 111 g/L (150 ~ 233), immunoglobulin IgA 2.03 g/L (1.0 ~ 4.2), immunoglobulin IgG 4.37 g/L (8.6 ~ 17.4), immunoglobulin IgM 0.47 g/L (0.5 ~ 2.8), immunoglobulin IgE 1 g/L (0 ~ 120), C3 0.51 g/L (0.7 ~ 1.4), C4 0.12 g/L (0.1 ~ 0.4), light chain KAPPA 1.3g/L (1.38 ~ 3.75), light chain LAMBDA 0.76g/L (0.93 ~ 2.42). Lymphocyte subgroup analysis (2020-9): lymphocytes percentage 3.97% (27.9 ~ 37.3), T lymphocytes percentage 93.15% (62 ~ 76.8), CD4+T lymphocytes percentage 19.04% (30 ~ 46), CD8+T lymphocytes percentage 71.57% (19.2 ~ 33.6), B lymphocytes percentage 4.09% (8.5 ~ 14.5), NK lymphocytes percentage 1.62% (9.5 ~ 23.5), CD4+/CD8+ 0.27 (0.57 ~ 2.44), Lymphocyte 2539 / uL (1752 ~ 2708), T lymphocyte 2365 / uL (1185 ~ 1901), CD4+T lymphocyte 483 / uL (561 ~ 1137), CD8+T lymphocyte 1817 / uL (404 ~ 754), B lymphocyte 113 / uL (180 ~ 324), NK lymphocyte 45 / uL (175 ~ 567). Liver function test results showed high liver enzymes and low albumin. Parathyroid hormone ：228.5pg/ml（15 ~ 65）. Blood calcium ：3.68mmol/L（2.11 ~ 2.52）. Blood inorganic phosphorus ：0.69mmol/L（0.85 ~ 1.51）. A series of tests for hepatitis, syphilis, and HIV infection were negative. There were no abnormal tumor markers.

Treatment after admission: The symptoms of myasthenia gravis were gradually improved after Intravenous steroid pulse(methylprednisolone 1000 mg/d, continuous intravenous infusion for 3 days, and then gradually reduce the dose) combined with gamma globule (400 mg/kg, intravenous injection for 5 days), tacrolimus (1 mg, three times a day). After admission, patients appeared chronic refractory non-infectious diarrhea and anemia, and were given symptomatic supportive treatment such as regulation of intestinal flora, blood transfusion, and human albumin infusion, and so on. Patients repeatedly developed the pulmonary infection, urinary tract infection, bacteremia, and septic shock while waiting for thymectomy, which led to myasthenia gravis crisis, aggravation of myasthenia gravis symptoms, and difficulty in weaning-off. Nervous system physical examination: Disuse atrophy of limbs, The muscle strength of the proximal limb of both upper limbs is 2 + grade, the distal limb muscle strength of double upper limb is 3 + grade, the muscle strength of proximal limb of both lower limbs is 0 grade, and the muscle strength of distal limb of both lower limbs is 2 grade. Immunological examination showed hypogammaglobulinemia, decreased B lymphocytes, decreased NK lymphocytes, and an inverted proportion of CT4+/CD8+ cells. GS was diagnosed. It is considered that the patient has thymoma, immunodeficiency, and frequent opportunistic infection, which leads to myasthenia gravis crisis. Despite the high risk of operation, the patient still underwent thymectomy. The patient underwent extended thymectomy through a median thoracic incision in October 2020, and the operation went smoothly. After the operation, it was confirmed that the pathological WHO classification of thymoma was type A, and the Masaoka-Koga stage was stage I. In order to reduce the risk of myasthenia gravis crisis and infection caused by surgical stress state, plasma exchange (once every other day, 5 times) was given before operation, and IVIg was given after operation. However, during the peri-operative period, the patients developed acute myocardial infarction with heart failure, anemia (hemoglobin 66g/L), and bilateral pleural effusion, which were improved after diuresis, blood transfusion, and thoracic puncture and drainage. After the operation, the muscle strength of the extremities of the patient was improved slightly, and there was no frequent infection recurred. He was discharged after weaning successfully. Physical examination at discharge: tracheotomy, a clear mind, the equal circle of bilateral pupils, about 3.5mm in diameter, sensitive to light reflex, isotropic movement of both eyes, forceful closure of eyelids, useless atrophy of limbs, cervical flexor muscle strength was grade 2, The proximal muscle strength of both upper limbs is grade 3, the distal muscle strength of both upper limbs is 4 +, the proximal muscle strength of both lower limbs is grade 2 -, and the distal muscle strength of both lower limbs is grade 2 +, moderate muscle tension of extremities, tendon reflex (+), double Babbitt sign (-).

3. Discuss

Our patient has MG and is treated with prednisolone (PSL) and tacrolimus (TAC). Because glucocorticoid inhibits cell-mediated immune response, reduces the number of T lymphocytes, monocytes, and eosinophils, inhibits the binding of the immunoglobulin to cell surface receptors, and reduces the concentration of complement and immunoglobulin. TAC is a powerful immunosuppressant, which inhibits T cell activation and T cell dependent B cell proliferation, and reduces the transcription and expression of lymphokines. The repeated bacterial and fungal infections of our patient, including Escherichia coli, Acinetobacter baumannii, Klebsiella pneumonia, Pseudomonas aeruginosa, Holderia onion, Candida albicans, and Candida tropicalis, may have been caused by the immunosuppressive treatment he received. However, after the glucocorticoid was gradually reduced and tacrolimus was discontinued, the patient continued to experience recurrent infections. Therefore, we considered that GS may exist in addition to immunosuppressive treatment-induced immunodeficiency. Subsequent immunological examinations, including serum immunoglobulin levels and lymphocyte subsets, confirmed the diagnosis of GS. This case emphasizes the need to consider the possibility of immunodeficiency caused by GS in MG patients associated with thymoma, rather than assuming immunosuppressive therapy-induced immunodeficiency. Before starting immunosuppressive therapy, the immunological examination should be

considered as part of the initial diagnostic evaluation for patients with MG and thymoma. In addition, of the 16 previously reported MG patients with GS, 7 patients developed GS symptoms after thymectomy. It may be due to the fact that the autoreactive T cells caused by thymoma have been distributed to the peripheral immune system before thymectomy, or the residual ectopic thymic tissue outside the thymus can not be removed[Error: Reference source not foundError: Reference source not foundError: Reference source not found]. It is suggested that even though the thymus has been removed, the possibility of GS still should be kept alert.

The identification of the characteristics of MG patients with GS is important for early recognition and appropriate treatment of GS. Delayed identification of GS may lead to infectious disasters. We summarize the demographic and clinical characteristics of our patients and previously reported MG patients with GS, which are listed in Table 1. The age of onset of MG in patients was 24 to 88 years, with an average age of 53± 18 years, and the ratio of male to female was 9:8. GS and MG were diagnosed simultaneously in 4 patients, and MG was diagnosed earlier than GS in 10 patients (average 11 years). The clinical manifestations of MG were reported in 13 patients, 77%(10/13) presented systemic myasthenia gravis, among which 38% (5/13) presented bulbar paralysis, 69% (9/13) had ocular muscle involvement, 8% (1/13) only involved the extraocular muscle, and 15%(2/13) presented myasthenia gravis crisis. The symptoms of myasthenia gravis were mostly improved after treatment with glucocorticoids and cholinesterase inhibitors. Takai et al. showed that MG patients with GS were more likely to get relief of MG symptoms when immunodeficiency occurs[Error: Reference source not found]. Both the case reported by Shiran and this patient had a myasthenia crisis caused by infection, and MG symptoms did not improve at the onset of GS. And all improved after thymectomy, intravenous immunoglobulin, plasma exchange, hormones, and anti-infection treatment. In our case, the second interesting finding is that there are multiple neuromuscular disease spectrum antibody positive, including anti-AChR antibodies, anti-skeletal muscle antibodies, anti-myocardial antibodies, anti-Titin antibodies. The anti-AChR antibody is a specific antibody of MG. Patients with positive AChR antibody often have thymic lymphoid follicular hyperplasia and thymoma. Titin antibodies are mainly found in patients with thymoma and late-onset, and are positively correlated with the severity of muscle weakness. In most of the previous cases, only the AChR antibody was positive. And our patient had multiple positive antibodies, suggesting that our patient was severe and had a relatively poor prognosis. Only 8 cases of thymoma were reported. Type B was the most common pathological type (4/8), followed by type A (3/8), and only 1 case of type AB thymoma was reported. Due to humoral and cellular immune dysfunction, chronic recurrent infection is the first symptom, pulmonary infection is the most common, followed by chronic diarrhea and autoimmune manifestations. Of the 17 patients, 13 cases (76%) had pulmonary infections, 8 cases (62%) had viral infections, most of them were cytomegalovirus, herpes zoster virus, herpes simplex virus, and 7 cases (41%) had fungal Infection, of which 4 cases (24%) developed oral candidiasis. diarrhea occurred in 4 cases (18%) and PRCA in 3 cases (18%).

At present, there is a lack of specific treatment for GS. The treatment of GS includes immunoglobulin, thymectomy, effective anti-infection, vaccination, and regulation of intestinal flora. Immunosuppressants can be used in patients with autoimmune diseases. Immunoglobulin therapy is the main means to control infection. Early identification and timely administration of immunoglobulin can reduce the incidence of future infection and improve the prognosis of patients. Among the 13 patients who received intravenous immunoglobulin, 8 patients had a reduced frequency of infection, suggesting the stable role of IVIg in GS treatment. IVIG is usually used once a month. Some researchers suggest that maintaining the valley value of serum immunoglobulin IgG > 5g/L can significantly improve the immune status of patients, reduce the incidence of infection and the use of antibiotics, shorten the length of hospital stay and reduce the mortality rate.

The effectiveness of thymectomy in the treatment of GS is still controversial. There have been reports of deterioration of the disease and aggravation of hypogammaglobulinemia after surgery[Error: Reference source not found]. Many scholars still suggest thymectomy, the integrity of tumor resection is the most important factor affecting the

prognosis of patients, although thymectomy can not correct hypogammaglobulinemia and improve immune function. 10 patients underwent thymectomy. Because of the invasion of the tumor, 2 patients received radiotherapy or chemotherapy after thymectomy, 3 patients only received radiotherapy and chemotherapy, and 4 patients were not treated. GS improved in 70% of patients who underwent thymectomy (7/10) and in 50% of patients who did not undergo thymectomy. The two patients with myasthenia gravis crisis, including this case, were not actively treated with thymectomy, and later all had myasthenia gravis crisis caused by infection, and the symptoms of MG, and the number of infections both improved after thymectomy. Before the start of drug therapy, thymectomy is the first-line treatment for MG with thymoma, and about 1/3 of MG patients with thymoma improve their myasthenia symptoms after thymectomy, suggesting that early thymectomy may benefit patients more. In order to remove the extrapericardial fat and vagal thymus tissue more thoroughly, our patients underwent extended thymectomy through the median thoracic incision. Despite active anti-infection and plasma exchange treatment before surgery and IVIg after surgery, our patient developed acute myocardial infarction with heart failure during the perioperative period. It suggests that perioperative management is critical for severe patients, and minimally invasive surgery may be a better choice. Our study shows that thymectomy is helpful to improve the condition. However, long-term follow-up is needed to determine the long-term effect of thymectomy.

MG patients with GS are more severe and have a worse prognosis than those without GS. The prognosis mainly depends on the frequency and severity of the infection. Through thymectomy, anti-infective, IVIg and other treatments, 59%（10/17）of the patients' symptoms improved, 29%（5/17）of the patients died of infection, and 6%（1/17）of the patients died of respiratory failure. Immunoglobulin replacement therapy is the main means to prevent infection. Delayed identification of GS may lead to infectious disasters and reduce the prognosis of patients. For patients with type B and A thymoma complicated with MG, especially middle-aged patients with systemic myasthenia gravis, GS, should be strongly suspected and lymphocyte subsets and immunoglobulin and complement examination should be performed when recurrent opportunistic infection occurs. Early thymectomy and intravenous immunoglobulin can improve the prognosis of patients.

Declarations

Consent for publication

Written informed consent was obtained from the patient’s family for publication of this case report .

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Table 1. Summary of 17 MG patients accompanied by GS in our and previously published cases

Case No.	sex	thymoma			MG				GS			
		Masaoka–Koga	Histologic type	treatment	onset age	clinical feature	Treatment	Outcome	Infectious disease	Complications	Treatment	Outcome
1	F	I	A	SR	57	Difficulty in swallowing and speaking, generalized weakness, dyspnea, neck flexion weakness	Prednisolone + pyridostigmine + IVIg + tacrolimus + plasma exchange	Improved	Recurrent bacterial and fungal infection(lung, bacteremia and urinary infection)	Diarrhea, anemia, hyperparathyroidism, pharyngitis	IVIg + broad spectrum antibiotics + plasma exchange + blood transfusion	Improved
2	M	ND	B3	SR+CT	ND	Weakness in the skeletal muscle	ND	ND	Recurrent visceral leishmaniasis		IVIg + liposomal amphothericin B	No change
3	M	ND	ND	SR	ND	ND	Prednisolone + tacrolimus	ND	Disseminated NTM infection(bacteremia, spondylitis, intestinal lumber abscess, lung and urinary infection)	Type 2 diabetes	IVIg + broad spectrum antibiotics	Died of the infection
4	M	IV	B2	SR	ND	Diplopia, abducens nerve palsy，partial ptosis, neck flexion weakness	Acetylcholinesterase inhibitors + orally administered glucocorticoids + plasma exchange	Improved	Pneumonia		IVIg + broad spectrum antibiotics	Improved
5	M	ND	ND	SR	65	Double vision, dysphagia, generalized weakness	Mycophenolate + pyridostigmine + oral prednisone (50 mg daily)	ND	Histoplasmosis + CMV colitis，pneumococcal infections，disseminated candidal infection	Hypertension	IVIg	Improved
6	F	IVa	B1	CT	62	Ptosis, weakness of abdominal muscles	Glucocorticoids	Improved	Bacterial pneumonia(staphylococcuus aureus, pseudomonas	PRCA, hyperthyroidism, depression	IVIg + broad spectrum antibiotics + blood	Died in pneumonia

									aeruginosa，neisseria species), oral candidiasis, HSV infection	,erythroderma，bronchiectasis	transfusion	
7	F	ND	ND	SR	53	ND	Intravenous steroid pulse + methotrexate	ND	Disseminated tuberculosis	Diabetes, anaemia, AOSD, MAS, HLH	IVIg + methotrexate + broad spectrum antibiotics + antituberculosis drugs + plasma exchange	Improved
8	F	ND	ND	Refused surgical resection	24	Pseudo-paralytic	Pirydostigminum bromide+neostigminum	ND	Pneumonia	Bronchiectasis, psoriasis	IVIg	Improved
9	F	III	ND	SR+CT+RT	36	Ptosis, dysarthria	Mycophenolate mofetil + pyridostigmine	ND	Cerebral toxoplasmosis + herpes zoster infection + oral candidiasis	Hypertension, dyslipidaemia	IVIg + nystatin + broad spectrum antibiotics + pyrimethamine +calcium folinate + sulfadiazine +prednisone + atovaquone	Improved
10	M	III	ND	CT+RT	45	ND	Prednisone + pyridostigmine	ND	Disseminated Nocardia farcinica infection（cutaneous、lung）	PRCA	IVIg + Cyclosporine + broad spectrum antibiotics	Improved
11	M	ND	B1	Refused surgical resection	88	Generalized weakness	Pyridostigmine	Improved	Recurrent HSV-2 infections(transverse myelitis，diffuse skin disease)	PRCA	Rituximab	Improved
12	F	IVB	ND	CT	35	Ptosis, limb weakness	Prednisolone	Improved	PML + cryptococcal meningoencephalitis + central venous portrelated	Erythrodermic psoriasis	IVIg + mirtazapine + mefloquine	Died of sepsis

									infections（candida albicans and staphylococcus epidermis）			
13	M	ND	ND	SR	ND	ND	ND	ND	Cytomegalovirus retinitis + *multiple chest infections* + *campylobacter septicemia*		*Acyclovir* + *ganciclovir* + *foscarnet*	Improved
14	F	ND	B	SR	29	Ptosis	Prednisone	Improved	Pneumonia(pseudomonas aeruginosa, CMV)，back infection with HZV	Diarrhea, bronchiectas	IVIg + *ganciclovir* + broad spectrum antibiotics	Improved
15	M	I	AB	SR	59	Ptosis, limb weakness	Pyridostigmine + prednisone	Improved	Recurrent infections of the respiratory(sterepto coccus pneumoniae), cutaneous and oral candidiasis	Adrenal tumors, pancreatic cancer	IVIg + broad spectrum antibiotics + antifungal therapy	Died in bacterial pneumonia
16	M	ND	A	Refused surgical resection	53	Difficulty in swallowing and speaking，ptosis	Pyridostigmine + prednisolone	Improved	Widespread CMV infection + herpes ofthe epiglottis + invasive eandidiasis + oral candidiasis + chest infection	Watery diarrhea, alopecia areata	IVIg + broad spectrum antibiotics	Died in upper gastrointestinal bleeding, melaena, bronchopneumonia and acute renal failure
17	F	ND	ND	Refused surgical resection	53	Muscle weakness, impaired deglutition, ptosis, diplopia	Neostigmine	Improved	Recurrent infections of the respiratory and urinary tract	Diarrhea, acute cholecystitis	Broad spectrum antibiotics	Died in respiratory insufficiency

SR, surgical resection; IVIg, intravenous immunoglobulin; ND, not described; CT, chemotherapy; RT, radiation therapy; NTM, nontuberculous mycobacterial; CMV, *cytomegalovirus;* AOSD, adult-onset Still's disease; MAS,

macrophage activation syndrome; HLH, haemophagocytic lymphohistiocytosis; HSV, Herpes simplex virus; PML, Progressive multifocal leukoencephalopathy.