ORIGINAL ARTICLE

GOODS'S SYNDROME: IMMUNODEFICIENCY BEYOND THYMECTOMY

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Thymic epithelial tumors, account for approximately 20% of all mediastinal neoplasms.[1]Thymomas may present with cough, chest pain, dysphagia, dyspnea, hoarseness, superior vena cava syndrome or Horner's syndrome. However, most cases are incidentally diagnosed in a chest imaging exam.[2,3,4]

Regardless of local invasion/ metastization, thymomas may be associated with a wide spectrum of immune-mediated clinical manifestations, and are frequent triggers of paraneoplastic autoimmune manifestations.[5,6] Good's syndrome (GS) or thymoma-associated immunodeficiency is characterized by hypogammaglobulinemia, reduced/absent B cells, decreased T-cells, an inverted CD4+/CD8+ T-cell ratio and reduced T-cell mitogen proliferative responses, that may precede or coincide with thymoma diagnosis.[2,6] In spite of GS being uncommon, around 6-11% patients with thymoma feature hypogammaglobulinemia, which is diagnosed during diagnostic work-up in patients with recurrent infections.[2,3,4]

In addition, it is also important to strengthen that 10% of adult-onset hypogammaglobulinemia cases have been found to be secondary to thymoma.[7]

Literature on GS is scarce, the authors herein report their experience on management of 9 patients withGSin a tertiary center for Primary Immunodeficiencies since 2010. Patients´ clinical, demographic and immunological features and thymoma TNM staging at diagnosis are summarized (table 1).[5,6]Age at onset of symptoms ranged from 38 to 71 years, (median 59 years), similar to studies in other countries.[8-10]GS was diagnosed following thymoma in 7 patients, in 5 of those an asymptomatic mediastinal mass was found. The other 2 patients presented with recurrent infections and identification of hypogammaglobulinemia led to thymoma diagnosis.

Regarding TNM staging, most cases were stage II and stage I thymomas. Single cases of stage IIIA and stage IVB thymoma were identified. As reported in other series, AB histological type was the most common (4/9), followed by type B, (3/9).[6,8] Surgical treatment was recommended to all and one patient refused. In addition, 4 patients were treated with radiotherapy and 1 with radio and chemotherapy.

All patients presented decreased serum immunoglobulin (Ig) G, 7 presented low serum IgM and 4 presented low IgA. IgG replacement was started in 6 patients up to 8 years after thymectomy and was refused by one patient.

Table 1 **Good Syndrome patients: Clinical features and immune profile upon diagnosis, treatment strategies and main complications throughout follow-up**

	Patient	1	2	3	4	5	6	7	8	9
	Gender	F	M	F	F	F	M	M	F	F
	Age at diagnose (years)	39	60	76	60	66	66	64	49	71
	First diagnosis (Th/H)	Th	H	Th	Th	H	Th	Th	Th	Th
	Time range between Th/H diagnosis	4 months	18 months	1 month	2 years	12 months	1 month	8 years	5 years	2 months
Thymoma	Masaoka-koga staging	IVB	III	IIA	I	I	IIA	I	IIA	IIA
Thymoma	TNM staging	pT4N2M1a	pT3N0M0	pT2N0M0	cT-1N0M0	pT1N0M0	pT2N0M0	pT1N0M0	pT2N0M0	pT2N0M0
Thymoma	Histology WHO classification	B1	AB	AB	-	AB	B1	AB	B2	A
Thymoma	Treatment	T, CT, QT	T, RT	T, RT	Refused	T, RT	T, RT	T	T, RT	T, RT
Hypogammaglobulinemia	IgG (mg/dL)*	516	274	321	660	478	665	518	704	529
Hypogammaglobulinemia	IgA (mg/dL)*	51	11	50	111	114	45	18	17	<5
Hypogammaglobulinemia	IgM (mg/dL)*	109	18	15	69	88	19	61	54	50
Hypogammaglobulinemia	Antibody response to vaccines#	Low (peptide antigen)	NA	Absent (peptide antigen)	Absent (both)	Normal	Normal	NA	NA	Absent (both)
Hypogammaglobulinemia	IG replacement (initiation)	Yes (before T)	Yes (before T)	Yes (before T)	No	No	No	Yes (8 years after T)	Yes (6 months after T)	Yes (before T)
Immune profile	CD3+ /µl (% within lymphocytes)	698 (92%)	2506 (78%)	713 (78%)	232 (93%)	1030 (88%)	684 (88%)	903 (93%)	1108 (88%)	1218 (81%)
Immune profile	CD4+ /µl (% within lymphocytes)	216 (28%)	680 (21%)	331 (36%)	1515 (61%)	734 (63%)	388 (50%)	290 (30%)	842 (67%)	263 (17%)
Immune profile	CD8+ /µl (% within lymphocytes)	488 (64%)	1570 (49%)	352 (39%)	916 (37%)	272 (23%)	259 (33%)	544 (56%)	232 (18%)	882 (58%)
Immune profile	CD19+ /µl (% within lymphocytes)	5 (0.7%)	120 (4%)	82 (9%)	NA	26 (2%)	13 (2%)	0.4 (0.1%)	5 (0.4%)	1 (0.1%)
Immune profile	CD3-CD56+ /µl (% within lymphocytes)	41 (5%)	574 (18%)	44 (5%)	NA	83 (7%)	48 (6%)	67 (7%)	1 (0.1%)	267 (18%)
Clinical features	Infectious complications	UTI; CD	EC; CD; systemic CMV; UTI	UTI; CD; systemic CMV	UTI	EC	Sino-pulmonary	Sino-pulmonary; EC; CD; systemic CMV	UTI; CD; systemic CMV	UTI; CD
Clinical features	Identified agents	C. jejuni, E.coli [stools] U. urealyticum [urethral exudate]	C. jejuni E. coli; K. pneumoniae [urine] H.pylori [stomach]	C. jejuni [stools]			H.pylori [stomach]	C. jejuni [stools]; H. influenza; S. pneumonia; C. koseri; E. cloacae [sputum]	K. pneumoniae [urine]	G.lamblia [stools] E. coli [urine]
Clinical features	Autoimmune complications		Psoriasis	PRCA	PRCA; RA; SjS	Pemphigus vulgaris	-	Pernicious anemia	Miastenia gravis; Vitiligo	Miastenia gravis
Clinical features	Neoplasic complications		-	Myelo-dysplasic syndrome		-	Prostate neoplasia	Gastric carcinoma		
Clinical features	Other complications		Malabsorption	BC; Gastritis	Severe osteoporosis	BC; Gastritis; Severe osteoporosis	Gastritis; CRS	BC; Gastritis; Malabsorption	Severe osteoporosis	BC; Gastritis
	Death (cause of death)	No	No	Yes (myelo-dysplasic syndrome)	Yes (unknown)	No	No	Yes (gastric carcinoma)	No	No
	Survival time after diagnosis (years)	4	4	6	1	3	3	4	2	1

F (female); M (male); Th (thymoma); H (hypogammaglobulinemia); T (Thymectomy); NA (Not available) CT (Chemotherapy); RT (Radiotherapy); Ig (Immunoglobulin); UTI (Urinary tract infection); EC (Esophageal candidíase); CD (Chronic diarrhea); CMV (Cytomegalovirus); PRCA (Pure Red Cell Aplasia); RA (Rheumatoid Arthritis); SjS (Sjögren's syndrome); CRS (Chronic Rhinosinusitis); BC (Bronchiectasis);

* Reference values: serum IgG 700-1600 mg/dl; serum IgM 70-400 mg/dl; serum IgA 40-230 mg/dl;

\# Response to both polysaccharide and peptide antigens was tested using pneumococcal polysaccharide and toxoid vaccines respectively.

Urinary tract infections were the most frequently reported, mainly by Escherichia coli or Klebsiella pneumoniae. Bronchiectasis were diagnosed in 4 patients.[8-10] Infections associated with T-cell deficiency were frequent, namely esophageal candidiasis (in 4 patients).[8-10] As reported in other series, chronic diarrhea was a major complication, affecting 6 patients, in association with Campylobacter jejuni infection in 4.[9,10]

Autoimmune complications were diagnosed in 7 patients, namely pure red cell aplasia (PRCA) and myasthenia gravis,diagnosed in 2 patients each, as previously reported.[3,8-10] Neoplastic conditions were diagnosed in 3 patients, namely gastric tumor, prostatic cancer and myelodysplastic syndrome.

As expected by literature reports and in contrast with patients with myasthenia gravis where a third improve after thymectomy, in our patients, there was no improvement in clinical manifestations or in hypogammaglobulinemia levels, after thymectomy.[7,8] Three patients died between 60 and 74 years. Two patients with AB thymomas died following myelodysplastic progression and gastric cancer.[5,6] A 60-years-old female died after refusing medical treatment or surgery. The 2 patients with PRCA diagnosis were in this group of poor outcome patients.

Our findings reinforce the importance of determining serum immunoglobulin levels in all patients with thymic tumors to ensure early diagnosis of GS. Moreover, in our series,GS morbidity and mortality have been mostly secondary to immune deregulation, rather than to thymoma itself, strengthening the relevance of continuous clinical surveillance in these patients.

Given the small number of presented cases and the scarce published evidence about the subject, itis not sufficient to make conclusions, but only to strengthen the relevance of prompt investigation of immunological dysfunction in patients with thymoma, in order to extend survival and improve quality of life upon diagnosis of GS. Thoracic surgeons play a major role not only in the management of thymomas but also in early diagnosis of hypogammaglobulinemia/immunodeficiency.

Conflict of interest:

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