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Graft *versus* Host-Like Syndrome Associated with Pure White Cell Aplasia 8 Years after Thymectomy: Case Report and Literature Review

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Abstract

Recently it was reported a small group of cases presented with diarrhea, elevated hepatic enzymes and skin rash associated with recurrent myasthenia gravis and thymoma. Thymoma-associated pure white cell aplasia is a rare and fatal condition. Few cases are reported that relate thymoma, recurrent myasthenia gravis and neutropenia. There is a speculation of circulated anticytokine auto-antibodies that may be directed to Granulocyte/Macrophage Colony Stimulating Factor (GM-CSF) receptor. Possible alteration to positive and negative T-cell selection disturbs the T-cell immunization and leads to uncontrolled auto-antibodies production. We report a case with recurrent myasthenia gravis, graft versus host-like disease and pure white cell aplasia along with a short literature review.

Keywords: GvHD-like syndrome; Pure white cell aplasia; Thymoma

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Introduction

Approximately 28% of patients with thymoma have Myasthenia Gravis (MG) and thymoma occurs in about 10% of patients presenting with MG [1]. Patients with thymoma have an increased incidence of several paraneoplastic syndromes. Except MG derived from the production of antibodies against acetylcholine receptor, several other immunologically mediated conditions are associated with thymoma and/or myasthenia gravis such as pure red cell aplasia, good syndrome, pemphigus, thyroiditis, type I diabetes and hypogammaglobulinemia [2-3]. The last 30 years few cases were reported with white cell aplasia related to antibody against GM-CSF production [1,2,4-6]. Wadhera et al. [7] in 2007 reported 8 cases with Graft *vs.* Host Disease (GvHD) like syndrome at the time of thymoma diagnosis and characterized by multiorgan attack. We report a case of "Thymoma-Associated Multiorgan Autoimmunity" (TAMA) admitted 8 years after thymectomy with recurrent myasthenia gravis, agranulocytosis with multiple positive immunological profiles that had an unfortunate fatal outcome. Using flow cytometry and short-term cultures we found an interesting T cell phenotypic profile and total inhibition of colonies growth.

Case Presentation

A 46-year-old woman presented with recurrent myasthenia gravis and previous thymectomy, 8 years ago. She admitted due to fever, diarrhea and vomiting. She had localized skin lesions looked like erythema nodosum spread centrifugally with central clearing. Chest auscultation revealed reduced breath sounds to the right lung base, abdomen was soft without pain and heart examination was normal with S1 and S2 clear and rhythmic. The patient also presented with tissue swelling of both leg extremities. The palpation did not reveal lymph nodes. Liver and spleen were not palpable. Patient's vital signs were normal.

Investigations on admission were as follows: CBC: Hemoglobin of 9.2 g/dL (normal 12 g/dL to 16 g/dL), platelet count of 216 × 10^9/L (normal 150 to 400 × 10^9/L). Her total WBC count was 1.37 × 10^9 /L (normal 3.8 to 10.5 × 10^9/L) with a neutrophil count of 0 × 10^9/L (normal 1.6 to 6.5 × 10^9/L) and lymphocyte count of 1.28 × 10^9 /L (normal 1.5 to 3.6 × 10^9/L). Renal and liver function tests were normal. The C-reactive protein was 7.7 mg/dL (normal <0.8 mg/dL) and ESR

Table 1: *In vitro* inhibition of hematopoietic progenitors of both erythroid lineage and granulocyte-macrophage colony forming cells by adding patient's serum. The inhibition was directly related to the dose of added patient's serum.

Colonies	Group A w/o serum	Group B 10 µl serum	Group C 50 µl serum	Group D 100 µl serum	Group E 150 µl serum
BFU-E	36 (38-40-30)	13 (16-10-14)	2 (2-3-1)	0	0
GM-CSF	9 (6-10-12)	1(1-1-1)	0	0	0
M-CSF	1,5 (1-0-4)	0 (0-0-0)	0	0	0
G-CSF	5 (4-7-4)	1 (2-0-1)	0	0	0

G-CSF: Granulocyte Colony-Stimulating Factor; M-CSF: Macrophage Colony-Stimulating Factor; GM-CSF: Granulocyte-Macrophage Colony-Stimulating Factor; BFU-E: Burst Forming Unit Erythroid. Zero represents scattered cells without forming colony

Table 2: Autoimmune diseases associated with thymoma.

Disease		Remission post-thymectomy	Reference
MG		Reduction in anti-ACH antibodies	[9,10]
SLE		Yes	[10,11]
SIADH		Yes	[12,13]
ARCA		Yes	[10]
BP		Yes	[10,14]
Others	Polymyositis, pernicious anemia, thyroiditis, hyperthyroidism, RA, UC, DM, scleroderma, Takayasu syndrome, Graves' disease, encephalitis	Unknown	[10,13,15,16]

ACH: Acetylcholine Receptor; ARCA: Acquired Red Cell Aplasia; BP: Bullous Pemphigoid; DM: Dermatomyositis; MG: Myasthenia Gravis; RA: Rheumatoid Arthritis; SIADH: Syndrome of Inappropriate Antidiuretic Hormone Secretion; SLE: Systemic Lupus Erythematosus; UC: Ulcerative Colitis

Table 3: Reported cases with thymoma-associated graft-versus-host-like disease.

Case Report	Age/Sex	Tumor	Myasthenia Gravis	Colitis	Skin Lesions	Abnormal Liver	Full Blood Count	Treatment	Outcome
Kornacki	20/M	Thymoma	No	Yes	No	No	No	Surgical Excision, Chemotherapy, autoBMT, radiation	Alive after BMT until submission
Holder	47/M	Spindle cell Thymoma	No	Yes	Yes	No	PRCA	Surgical Resection, IVIG, transfusion, cyclosporine	Unknown
Wang	38/F	Metastatic Thymoma	Yes	Yes	Yes	Yes	No	Surgical resection, chemotherapy, steroids	Died From infection
Lowry	35/F	Metastatic Thymoma	Yes	Yes	Yes	No	No	Surgical resection, chemotherapy, steroids, IVIG, plasmapheresis, octreotide	Died from her malignancy
Sader	46/M	Invasive Thymoma	No	Yes	No	No	No	Surgical resection, steroids, radiation	Unknown
Sleijfer	57/F	Locally Invasive	No	Yes	Yes	Yes	No	Surgical resesction, IVIG, steroids	Died From infection
Wadhera	50/M	Locally Invasive	No	Yes	Yes	Yes	No	Surgical resection, chemotherapy, steroids, IVIG, PUVA, octreotide	Died From infection
Current case	46/F	Thymectomy 8 years ago	Yes	Yes	Yes	No	PWCA	IVIG, high dose steroids	Died From infection

Auto BMT: Autologous Bone Marrow Transplantation; F: Female; IVIG: Intravenous Immune Globulin; M: Male; PWCA: Pure White Cell Aplasia; PRCA: Pure Red Cell Aplasia; PUVA: Psoralen Plus Ultraviolet A

was 60 mm (normal <20 mm). Additional investigations showed low level of Immunoglobulin G (IgG), and IgA and normal IgM level. An autoimmune profile was performed that included antinuclear antibody, double-stranded DNA antibodies and anti-smooth muscle antibody all of which were positive, C3 and C4 were low. Thyroid function tests showed low level of TSH with slightly increased FT_3 and FT_4 and clotting tests were normal. Investigating the diarrheal syndrome, stool cultures were negative along with the blood analysis for *Shigella* and *Salmonella*. *Clostridium difficile* test was also negative. Viral tests for CMV and EBV were negative for current infection. Blood cultures revealed infection from *Stenotrophomonas maltophilia* sensitive to many categories of antibiotics.

Computed tomography scan showed chest infection of right lung base and small pleural bilateral effusion. Chest X-rays showed right hemi-diaphragmatic elevation while abdominal ultrasound was normal. The patient was immediately covered with wide spectrum antibiotics and granulocyte growth factors. Consultations from surgeon, neurologist, rheumatologist, dermatologist and cardiologist were also requested. Colonoscopy was recommended when the situation of the patient would allow it. Dermatologist examination was positive for subacute nodular migratory panniculitis of Vilanova and Piñol. Expertise meeting concluded that clinical and laboratory results indicated the presence of circulated autoimmune antibody directed simultaneously to multiple targets. It appears that clinical features of diarrhea associated with skin lesions leads to a syndrome that resembling GvHD-like disease. Unfortunately, a colonic or skin biopsy specimen to confirm the presence of colitis or GvHD-like dermatitis was not pursued in our patient mainly because of poor functional status, suppressed immune status, and no apparent impact on treatment.

Simultaneously, Bone Marrow (BM) aspiration and biopsy were performed to exclude an underlined hematologic malignancy. BM revealed a nearly complete absence of granulocytes precursors with normal maturation of erythroid and megakaryocytic lineages. Lymphoid population was proportionally increased with normal ratio CD4:CD8. Peripheral blood cytometry had been assessed by standing surface expression antigens especially on T-cells. We therefore analyzed the phenotype of peripheral blood T-cells that presented the 81% of the mononuclear cells. Seventy three percent of CD3+ was also CD8+. Interestingly, the majority of the CD3+ CD8+ cells co expressed CD45RA and CD27 which made them similar to naïve T-cells. In order to evaluate the effect of patient's serum in blood cells we performed short term cultures in methylcellulose with and without patient's serum. Mononuclear cells (2×10^5/ml) were

isolated from peripheral blood sample of three voluntary healthy donors by centrifugation with Ficoll-Hypaque (Sigma St Louis, MO, USA) and were placed on culture dishes coated with methylcellulose (Methocult HC4435, Stem Cell Tegnologies, Vancouver, Canada). Short term cultures without patient's serum comprised the control group (Group A), while short term cultures with patient's serum in different doses (10 μl, 50 μl, 100 μl and 150 μl) comprised the test sample (Group B, C, D and E). The cultures were incubated at 37°C for 14 days in 5% CO_2. Two independent investigators evaluated the number of hematopoietic progenitor cells per dish. Samples were viewed with an inverted fluorescent microscope (Axiovert 25, Zeiss AG, Göttingen, Germany). We observed *in vitro* inhibition of hematopoietic progenitors of both erythroid lineage and granulocyte-macrophage colony forming cells. The inhibition was directly related to the dose of added patient's serum (Table 1).

The patient chest infection rapidly progressed despite the multiple antibiotic combinations including empiric antifungal agent administration. Corticosteroids and intravenously immunoglobulins administration could not reset absolute neutrophil number to normal state. The patient was intubated and transferred to the intensive care unit where she died with multiorgan failure due to infection 3 weeks after her admission.

Discussion

The thymus is a lymphatic organ located in the anterior mediastinum which is responsible for many immunological functions, including the production of mature, functional T cells and the induction of self-tolerance. Thymoma is the most common malignancy that originates from the thymus gland and accounting for 50% of anterior mediastinal tumors [8]. Current scientific evidence relates several autoimmune diseases with thymoma (Table 2) [9-16], and defective immune regulation has been suggested to be the link between these diseases. The time of the diagnosis of autoimmune disorder widely varies. In 30% of patients with thymoma, autoimmune diseases will be found either in a comorbid state or after thymectomy, where up to 50% of patients are diagnosed simultaneously with two autoimmune diseases [17].

Myasthenia Gravis (MG) considered as the commonest autoimmune disease that is related with thymoma. MG auto antibodies were found to be directed against the Acetylcholine Receptor (AChR) in the neuromuscular junction of skeletal muscles [18]. 75% of patients with MG have some degree of thymus abnormality, including thymic hyperplasia in 85% of those patients and thymoma in 15% of cases [19]. The co-existence of Systemic Lupus Erythematosus (SLE) and thymoma differs between 1.5% and 2% in clinical epidemiological studies and up to 10% in cases where thymus biopsies were studied [11]. Furthermore, in some patients this co-existence of SLE and thymoma was associated with poor prognosis [11]. The close relation between these two diseases is highlighted by the remission of steroid therapy-resistant SLE disease observed post-thymectomy [20]. Other studies have described that polyarthritis, skin rashes, fever and cytopenias are frequent in SLE patients with thymoma [21]. Thus, it seems that although the exact mechanisms underlying both pathologies are still unclear, the association between thymoma and SLE is arguable [22].

Hematological manifestations are also observed in patients with thymoma, highly associated with immune dysfunction. Acquired pure red cell aplasia is the commonest cytopenia that will be demonstrated with thymoma. Impairment of erythroid progenitors or precursor cells seems to be T cell-mediated, and it is estimated that 5% of thymoma coexist with pure red cell aplasia [23]. In several studies including histological analysis of thymoma from patients diagnosed with pure red cell aplasia, small germinal centers and lymphoid aggregation were demonstrated in their bone marrow [17]. This suggests a link between humeral and cellular alterations observed in these patients. Other immune-mediated cytopenias, such as thrombocytopenia and neutropenia, were also reported in combination with thymoma [17]. Pure white cell aplasia is reported in few cases with thymoma. The co-existence with other autoimmune diseases and the remission with immunosuppressive therapy are considered as indirect proof of an underlying autoantibody production. In few studies autoantibodies against granulocyte-macrophage colony stimulating factor were found that could also explain the absence of myeloid lineage that was present in bone marrow biopsies [1].

Dermatological manifestations are also observed in patients with thymoma. Many dermatological diseases are associated with thymoma such as pemphigus a, paraneoplastic pemphigus and bullous pemphigoid [10,14]. More than 20 cases of pemphigus have been reported in the past several decades [24], and in a recent case study, thymectomy resulted in regression of bullous dermatoses [25]. Interestingly, there are reports of skin lesions associated with thymoma resembling GVHD skin lesions. There have been 7 reported cases of thymoma associated GVHD-like disease [7]. All of the cases involved the gastrointestinal tract. In 5 out of 7 reported cases morbilliform eruption on biopsy specimen was consistent with acute GVHD. Hypogammaglobulinemia was seen in each 3 of the 7 patients, whereas three patients had abnormal liver enzyme levels, especially alkaline phosphatase, that reveals a hepatic involvement to the GVHD-like disease. All patients were reported to have chronic diarrhea with negative stool culture findings, among them four patients had colonic biopsy specimens that showed a GVHD-like colitis. Five patients died of serious infections. Thus, it appears that the development of a GVHD-like eruption in a patient with thymoma foreshadows a progressive disease with a fatal outcome (Table 3) [7].

The etiology of many autoimmune diseases appears to be a combination of factors that usually involves genetic propensity and another factors, such as the environment, immune-mediated processes, infections, hormones and drugs [26,27]. In the case of the thymus and autoimmunity, it is rational to conjecture that the underlying mechanism is based on a dysregulation in immune function. Progenitor T cells, like B cells, are produced in the bone marrow; however, they later migrate to the thymus for a series of normal procedures including maturation, differentiation and selection. T-cell maturation in the thymus consists of, as expected, rearrangements of the germ-line T-cell receptor genes and the expression of various membrane markers. Along with T-cell modification and maturation into an effective group of lymphocytes, a meaningful pair of selection is happening in the thymus. Positive selection allows the survival of the T cells whose T-cell receptors can recognize self Major Histocompatibility Complex (MHC) molecules. Alternately, negative selection rejects T cells that respond forcefully with self-MHC or with self-MHC plus self-peptides, thus eliminating autoreactivity of these T cells [26]. These thymic functions are important to eliminate auto-reactivity, to maintain self-tolerance and to enhance the production of regulatory T cells [26]. These cells represent a specific subset of T cells which dominantly control auto-reactivity in the periphery. Based on these observations, the

association of thymoma with loss of self-tolerance is rational, and several mechanisms have been proposed based on the hypothesis that the abnormal thymus produces impaired T cells [28].

The combined cellular and humeral dysregulation theory suggests a connection between the adaptive arms of the immune system that permits them to act together in order to support autoimmune disease. The export of auto-reactive T cells from thymus to the periphery is supposedly a critical step in the thymoma-associated autoimmunity; on the other hand, an additional step has been reported as necessary to bond these auto-reactive T cells to autoantibody-producing B cells. This suggested model is consisting of two independent steps [29]. The first contains a great number of CD8 T cells produced by thymus to exhibit impaired tolerance, thus initiating an autoimmune cascade. However, during the second step, the humoral immunity succeeds the cellular by activating CD4 T cells, which, in turn, stimulate B cells to produce autoantibodies. This mechanism could explain the over-production of autoantibodies in patients with thymoma or myasthenia gravis [29].

Recently peripheral flow cytometry to a patient with thymoma, pure white cell aplasia and autoimmune thyroiditis showed the presence in the peripheral blood of CD8+ T cells that expressed a homogeneous naive phenotype. CD8+ CD45RA+ CD27+ T cells represent the majority of CD8+ T cells in cord or newborn blood, whereas their number decreases with age along with antigen encounter and immunological experience. Thus, after the age of 50 year, they represent less than 50% of total CD8+ T cells, the others being memory CD45RA–CD27+ and effector CD45RA+ CD27– cells. Phenotypic analysis performed 2 and 4 months post-thymectomy to the patient showed no changes in CD8 and CD4 subset population. These data indicate a remaining alteration in the composition of T cells of the patient's peripheral blood. Thus, it can be speculated that pre-T cells may create a neoplastic thymus where they can be matured [2].

In order to distinguish the reaction of different T-cells subsets on GVHD onset, Dutt et al. [30] in 2007 reported that naïve T-cells resulted acute colitis characterized by severe diarrhea, rapid host weight loss and death. On the other hand, memory T-cells cause chronic pattern of liver and colon injury that isn't associated with early diarrhea and weight loss. The paradoxical ability of naïve T-population to induce rapid and acute type of GVHD than effector memory T-cells is probably due to different trafficking and expansion capacities of the two T-cell subsets [30].

In our patient, severe diarrheic syndrome, agranulocytosis and skin lesions were present in admission. She rapidly developed severe lung infection and multiorgan failure that led to her death. Bearing in mind her medical history of thymoma, it seems that the patient developed GVHD-like disease characterized by colitis, skin lesions, normal hepatic function and hypogammaglobulinemia. It was also accompanied with agranulocytosis and positive autoimmune profile similar with this observed in SLE. According to our knowledge this is the first case report with GVHD-like disease associated with agranulocytosis and SLE diagnosed eight years after thymectomy. Studying the lymphoid population of patient's peripheral blood we observed an interesting increased number of naïve T-cell population that confirmed the suspicion of T-cell dysregulation, happened probably in bone marrow that disturbs the control of autoreactivity. The production of different types of antibodies attacking several parts of the body induces a phenotype similar with that we observe in GVHD after allogeneic transplantation. Simultaneously, the possibly production of antibody against GM-CFU, indirectly proved by *in vitro* cultures, causes the agranulocytosis. Unfortunately, the rapid aggravation of patient clinical status did not allow us to proceed to biopsies that would show typical histopathological organ injuries that would reinforce the diagnosis of GVHD-like disease.

Conclusion

In conclusion, GVHD-like disease is a rare multiorgan autoimmune disease that is associated with thymoma at diagnosis as well as after thymectomy. Dysfunction in selection process permits to lymphoid population to react abnormally against antigen that should be recognized as familial. It is likely that the pathophysiology of HSCT-associated GVHD is similar to that seen in thymoma-associated multiorgan autoimmunity. Theoretically, self-reactive deregulated T cells, originating in the thymoma, are responding similarly to grafted allogenic lymphocytes. Dermatologists, hematologists, oncologists, gastroenterologists, and pathologists should maintain a high index of suspicion for TAMA in patients with thymoma, who have a morbilliform skin eruption, chronic diarrhea, abnormal liver enzymes associated with other immune paraneoplastic syndromes.

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