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Graft-versus-host disease-like erythroderma: a manifestation of thymoma-associated multiorgan autoimmunity

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Abstract

Thymoma associated multiorgan autoimmunity is a rare paraneoplastic disorder, clinicopathologically similar to graft versus host disease, which is thought to be mediated by dysfunctional negative thymocyte selection and abnormally low levels of T_{regs}. We report a 50 year old Chinese woman with a history of malignant thymoma and myasthenia gravis who developed graft versus host disease-like erythroderma after instituting chemotherapy and undergoing myasthenia crisis. Clinically her rash presented as erythematous scaly papules, which evolved to psoriasiform patches and plaques with foci of vitiligo. Histopathologically the biopsy showed a predominantly interface dermatitis with necrotic keratinocytes extending to the upper levels of the epidermis, and florid basket weave orthokeratosis. Clinical and laboratory work-up ruled out common inflammatory or infectious causes, eventually favoring the diagnosis of TAMA with GVHD-like erythroderma. Unfortunately, the patient underwent multi-organ compromise and death due to respiratory failure from myasthenia crisis. Patients with TAMA have a poor clinical outlook; rare successful treatments include high dose oral steroids and additional modalities including bone marrow transplant and chemotherapeutic or biologic agents. As the predominant findings are in the skin, dermatologists and dermatopathologists are in a unique position to enable the early diagnosis and treatment of this unusual disease.

Thymomas are tumors of thymic epithelial cell origin and are the most common type of thymic neoplasm. They are often diagnosed incidentally on imaging, but can also present with thoracic mass effects such as cough, chest pain, and phrenic nerve palsy. Additionally, thymomas are frequently associated with paraneoplastic autoimmune disorders, the most common of which are myasthenia gravis, pure red cell aplasia, and hypogammaglobulinemia. While rare, several case studies^{1–13} have also reported a condition termed thymoma-associated multiorgan autoimmunity (TAMA) affecting the skin, liver, and colon. Interestingly, the histopathologic findings in damaged organs resemble those of graft-versus-host disease (GVHD) despite the lack of transplanted lymphocytes. GVHD-like erythroderma is rare and little is understood about its pathogenesis. Additionally, its

histopathologic presentation is similar to that of a drug eruption or viral process. As a result, diagnosis can be difficult, and treatment decisions become rooted in speculation.

Herein, we report the case of a 50-year-old Chinese woman with a past medical history of malignant thymoma and myasthenia gravis who was admitted for myasthenia crisis and found to have GVHD-like erythroderma. Four years prior to this admission, the patient presented to her physician with complaints of dysphagia, generalized fatigue, and muscle weakness. She was diagnosed with myasthenia gravis, and a computerized tomography (CT) scan done on workup revealed a 4.1×3.9 cm mass located in the anterior superior mediastinum. The tumor, measuring 8.1 cm, was resected three months later and histopathologic analysis revealed a stage IIA, type B1 thymoma (fig 1) with positive margins. All six sampled lymph nodes were negative for metastatic disease. Tracheal stenosis was also noted during the procedure. Three months after tumor resection, the patient underwent radiotherapy and completed 24 of the planned 30 doses, but chose not to finish treatment due to worsening symptoms of cough, dysphagia, and extreme fatigue. The patient was managed expectantly for two years. Surgical correction of the tracheal stenosis was considered during that time, but the patient refused treatment. Unfortunately, five months prior to admittance, a follow up CT scan revealed a 4.4×2.1 cm paratracheal mass and several smaller pleural-associated masses. The patient was also noted to have vitiligo at that time. Surgery was not considered to be an optimal treatment due to complications that might arise in the setting of the patient's tracheostenosis and the possibility of incomplete excision. Following physician recommendation, the patient elected to receive chemotherapy with cyclophosphamide, doxorubicin, and cisplatin. She tolerated the first cycle very poorly, experiencing symptoms of increasing dizziness, significant nausea, vomiting, worsening dysphagia, and intermittent epigastric, abdominal, and chest pain. Chemotherapy was discontinued, and the patient continued on pyridostigmine only. Shortly after, she experienced three weeks of worsening dysphagia, fatigue, and muscle weakness. The patient presented and was hospitalized for myasthenia crisis. Her breathing status decompensated requiring intubation and later tracheostomy with mechanical ventilation. Treatment for myasthenia crisis included pyridostigmine, methylprednisolone, and plasmapheresis.

While hospitalized, the patient was also found to have a pruritic rash on her trunk and extremities of 3–4 weeks duration with recent spread to lower abdomen and groin. Examination revealed scattered erythematous papules with collarettes of scale. Additionally, the right breast was noted to have an eczematous patch with fine scaling. No burrows, vesicles, or pustules were seen. The initial differential diagnosis included scabies with eczema reaction, dermatitis herpetiformis, and pityriasis rosea. A punch biopsy of a papule on the abdomen was performed, and the initial pathology reading was of an interface and perivascular dermatitis with necrotic keratinocytes throughout the epidermis (figs 2,3) and follicular epithelium (fig 4) as well as basket-weave orthokeratosis. Subsequent periodic acid-Schiff (PAS) staining showed a slight increase in basement membrane thickness while colloidal iron staining demonstrated a slight increase in connective tissue mucin. These findings ruled out scabies and added drug eruption, viral process, pityriasis lichenoides, autoimmune process, and connective tissue disease to the differential diagnosis. Pityriasis rosea was decided to be the best clinical diagnosis, though there was a lack of histopathologic correlation. The patient was prescribed triamcinolone and Lidex, which was

applied inconsistently without improvement. During this time the patient also developed ventilator-associated pneumonia that persisted through the patient's hospital course despite broad antibiotic treatment. After approximately six weeks, the dermatology service was consulted again to reevaluate the patient's persistent rash. Examination showed erythematous patches with peripheral scale on the patient's back and erythematous, flat-topped papules with overlying scale on the upper and lower extremities. The involvement on the arms had a somewhat guttate appearance. Extensive involvement of wrists bilaterally and some 'koebnerization' was observed. Overall, the eruption had a more disseminated psoriasiform appearance compared to the lichenoid eruption observed on initial consult. Because of these findings, guttate psoriasis and lichen planus were considered. Subsequent ASLO (define) and culture tests were negative ruling out streptococcal-related guttate psoriasis. Additionally, evidence of scratching and a lack of oral mucosa and nail involvement made lichen planus less likely. Psoriatic drug eruption was also considered but was excluded by medication history. Lastly, the clinicopathologic features and history of lansoprazole use suggested possible drug-induced subacute cutaneous lupus erythematosus (SCLE). However, autoimmune workup revealed negative anti-Ro and anti-La antibodies and positive anti-dsDNA antibodies.

Considering the clinicopathologic features and after a review of the literature, the patient was deemed to have a TAMA with GVHD-like erythroderma. During this time liver function tests continually declined and aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase levels became markedly elevated, which was believed to be due to the patient's TAMA. The patient died three weeks later due to respiratory failure following patient-requested extubation.

The pathophysiology of thymoma-associated paraneoplastic disorders is not completely understood, but the available evidence implicates changes in various mechanisms of T-cell maturation. Normally, the thymus controls thymocyte development through processes of positive and negative selection that depend on T cell receptor (TCR) affinity for major histocompatibility complex (MHC). During positive selection, thymocytes that are non-reactive toward the MHC-antigen complex on cortical epithelial cells undergo apoptosis. Surviving thymocytes migrate to the corticomedullary junction where antigen presenting cells (APC) and medullary thymic epithelial cells (mTEC) again present self-antigens on MHC peptides. Thymocytes that react too strongly to these complexes are eliminated. Negative selection depends on expression of the autoimmune regulator (AIRE) gene by mTEC. AIRE drives ectopic expression of peripheral self-antigens, which contributes to central tolerance. Moreover, some thymocytes that have intermediate reactivity at the negative selection stage develop into regulatory T-cells (T_{regs}), which also contribute to central tolerance. Alterations in these processes can cause severe autoimmunity such as autoimmune polyendocrine syndrome type 1 (APS-1) and immune dysregulation, polyendocrinopathy, enteropathy X-linked (IPEX) syndrome. In thymomas, positive selection appears to remain intact as CD4+/CD8+ thymocytes—the products of positive selection—are abundant¹⁴. However, various abnormalities potentially interfering with negative selection have been found in patients with thymoma-associated autoimmune disease including decreased AIRE expression^{8,15,16}, lack of medullary features¹⁷, and decreased MHC class II expression¹⁷. These findings suggest that thymoma-associated

autoimmune processes may develop partly from the systemic release of self-reactive effector T-cells. Moreover, thymoma patients have been observed to have lower levels of peripheral and thymocytic T_{regs},^{8,11,16} which is thought to further contribute to autoimmunity in those patients.

Among the paraneoplastic disorders associated with thymoma, our patient exhibited myasthenia gravis and GVHD-like erythroderma. While myasthenia gravis is common among thymoma patients, cutaneous GVHD-like symptoms are not. Classic GVHD requires allogenic transplantation of lymphocytes into an immune-insufficient host, which occurs most often in the setting of hematopoietic stem cell transplantation (HSCT). In GVHD, grafted lymphocytes most commonly damage the skin, liver, gastrointestinal tract, lungs, eyes, and oral mucosa^{18,19}. In thymoma patients, GVHD-like damage occurs in the liver, colon, and skin – and this represents the syndrome termed TAMA.

Sixteen separate cases of TAMA have been reported in the literature to date. Of those cases, 12 exhibited GVHD-like erythroderma^{2-4,6-13}, 5 exhibited liver involvement^{3,6,8,9,11}, and 10 exhibited GVHD-like colitis^{1-6,8,9}. Additionally, 5 cases reported skin involvement only^{7,10-13} and 4 cases reported colitis only^{1,5,8}. No cases have been reported that only involve liver damage. Our patient had skin involvement and signs of liver damage. In the reviewed cases, common clinical descriptors for the cutaneous eruptions included pruritic, scaling, morbilliform, erythrodermic, papulosquamous, and psoriasiform. Eruptions were almost always widespread, involving the trunk, extremities, and head. Oral erosions were also observed in multiple cases. Our patient presented with an intensely pruritic papulosquamous eruption that became somewhat psoriasiform and involved the trunk and extremities. Our patient also had vitiligo. The most common pathologic findings of GVHD-like erythroderma were parakeratosis, necrotic keratinocytes, and interface and perivascular dermatitis. Less common pathologic findings included spongiosis, liquefaction degeneration, and acanthosis. These features are consistent with classic GVHD^{20,21}. The timing of cutaneous presentation ranged from being the symptom that led to a diagnosis of thymoma to occurring 18 years after the diagnosis of thymoma. When these clinicopathologic features are observed in thymoma patients who have not undergone HSCT, transfusion of non-irradiated blood, or solid organ transplantation, TAMA should be strongly considered as a diagnosis. Drug eruption and viral processes can have similar histopathologic features and should also be ruled out.

TAMA patients typically have a poor clinical course. Of the 16 cases we reviewed, 8 patients died^{3,4,6-9,11,13}, usually due to infection. In 4 other cases^{2,5,8,11} the outcome was not reported. Only 4 cases^{1,8,10,12} reported that the patient was alive at last follow up or in remission. Our patient died of respiratory failure related to myasthenia gravis. In previous cases, treatment for GVHD-like erythroderma usually involved high dose oral and topical steroids, which had variable effect. Addition of cyclosporin or ultraviolet therapy seemed to be beneficial in some cases^{7-9,13}, but the eruptions usually returned when treatment was tapered. The four successfully treated patients received the following therapies: steroids and bone marrow transplant¹; steroids and bone marrow transplant⁸; steroids, mycophenolate, and PUVA therapy¹⁰; and steroids, carboplatin, and paclitaxel¹². Our patient's condition did not improve with topical triamcinolone and Lidex nor did it improve with

methylprednisolone given for myasthenia. A more thorough understanding of the pathogenesis of TAMA is needed to find treatments with more consistent and durable results.

In summary, the clinicopathologic features of cutaneous TAMA are similar to those of GVHD. Little is known about the pathogenesis of TAMA, but studies implicate dysfunctional negative thymocyte selection and abnormally low levels of T_{regs}. Because skin involvement has been the most common presentation in reported cases of TAMA, we posit that dermatopathologists are in a unique position to expedite diagnosis and help guide treatment.

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Figure 1. Hematoxylin and Eosin, 100x original image, thymic cortical epithelial cells with epithelioid morphology alternate with thymic lymphocytes in this lobulated tumor.

Figure 2.

Hematoxylin and Eosin, 100x original image, prominent hyperkeratotic basket weave stratum corneum overlies an epidermis overtaken by necrotic keratinocytes at all levels, associated with vacuolar interface alteration and exocytosis of small lymphocytes.

Figure 3.
Hematoxylin and Eosin, 200x original image, the follicular epithelium is notably involved by keratinocyte necrosis.

Figure 4.
Hematoxylin and Eosin, 400x original image, interface dermatitis with exocytosis and necrotic keratinocytes extending into the upper levels of the epidermis.