

Thymoma-associated multiorgan autoimmunity initially manifested by graft-versus-host disease–like erythroderma: Case report and possible therapeutic role of antimalarial drugs



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INTRODUCTION

Thymomas are associated with various autoimmune and paraneoplastic processes. Thymoma-associated graft-versus-host disease (GVHD)-like erythroderma is rarely reported, and the pathogenesis is incompletely understood. Here we report the case of a patient with metastatic thymoma who presented with GVHD-like erythroderma unresponsive to cyclosporine or prednisone. He was treated with modified Goeckerman therapy (MGT), intravenous immunoglobulin (IVIg), and hydroxychloroquine. We review the mechanism of GVHD-like erythroderma and propose a therapeutic role for antimalarial drugs.

CASE REPORT

A 55-year-old man with metastatic thymoma complicated by myasthenia gravis and pure red cell aplasia presented to the emergency department for evaluation of a rash. The rash began 2 weeks prior to presentation, starting on his head and neck, and quickly generalized. The patient reported chills but denied other systemic symptoms. Metastatic thymoma was diagnosed 5 years prior. Treatment at time of diagnosis consisted of 4 cycles of carboplatin and etoposide (October 2011 to January 2012) with resulting stability but persistent disease activity. He started palliative radiation to pleural metastases 2 weeks prior to the onset of the rash.

Abbreviations used:

GVHD:	graft-versus-host disease
IVIg:	intravenous immunoglobulin
MGT:	modified Goeckerman therapy
TAMA:	thymoma-associated multiorgan autoimmunity
TLR:	Toll-like receptor

Physical examination found confluent, erythematous and scaly plaques distributed over the face, trunk, and extremities with diffuse desquamation, involving approximately 85% of his total body surface area (Fig 1, A) with areas of sparing (Fig 1, B). There was no mucosal involvement. At time of consultation, he was receiving pyridostigmine, 60 mg 4 times daily, cyclosporine, 175 mg twice daily, and prednisone 15 mg/d; these were initiated over 3 years prior to presentation.

Histopathologic examination of 2 punch biopsy specimens found a vacuolar interface dermatitis with apoptotic keratinocytes and parakeratosis (Fig 2) consistent with GVHD.¹ This patient had not undergone stem cell transplantation, blood transfusion, or solid organ transplantation. Given the presence of a GVHD-like skin eruption and metastatic thymoma, the diagnosis of thymoma-associated GVHD-like erythroderma was made.

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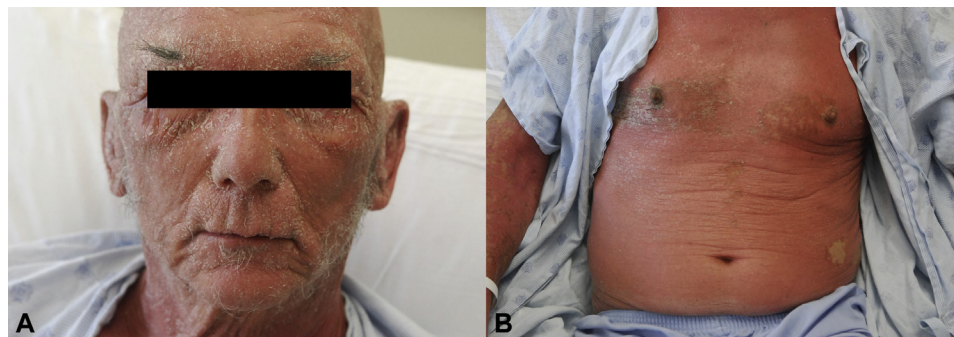


Fig 1. GVHD-like erythroderma. **A** and **B**, Confluent, erythematous, and scaly plaques on the face and areas of sparing on abdomen.

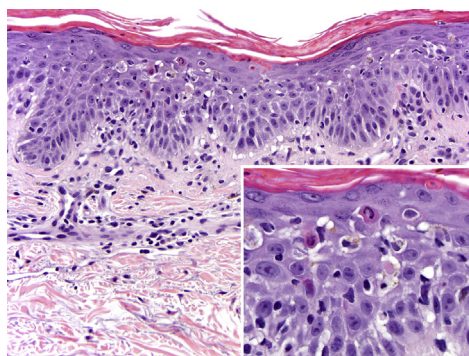


Fig 2. GVHD-like erythroderma. Histopathology shows parakeratosis, apoptotic keratinocytes, and vacuolar interface dermatitis. (Hematoxylin-eosin stain; original magnifications: $\times 100$; inset, $\times 400$.)

The patient was admitted for MGT. The erythema improved slightly with treatment. Chemotherapy was not pursued because of failure to thrive secondary to radiation-induced dysphagia. He was discharged on his home dose of cyclosporine, 175 mg twice daily, and prednisone, 40 mg/d, with minimal improvement. Two weeks later, he was re-admitted for worsening rash. During this admission, in addition to a repeat course of MGT, he was treated with 2 g/kg total of IVIg and started on hydroxychloroquine, 200 mg twice daily, which he continued on discharge. Although his skin improved, the patient had several complications, including esophageal/gastric dysmotility and infection. Cyclosporine was discontinued, prednisone was reduced to 20 mg/d, and hydroxychloroquine was continued at the same dose. At 1-month follow-up, his skin had continued improvement. Unfortunately, the patient's functional status declined. He died of multiple organ failure secondary to pneumonia approximately 4 months after his first admission to the hospital.

DISCUSSION

Thymoma is the most common neoplasm arising from the thymus and is associated with autoimmune and paraneoplastic disorders, most commonly myasthenia gravis, pure red cell aplasia, and hypogammaglobulinemia.² Rarely, a GVHD-like eruption can occur in patients with thymomas as a manifestation of thymoma-associated multiorgan autoimmunity (TAMA). TAMA is characterized by cutaneous, liver, and gastrointestinal manifestations with dermatopathologic features that resemble GVHD. Most patients have gastrointestinal and hepatic involvement, although skin lesions can occasionally be the only presenting feature.³ Current evidence suggests cutaneous manifestations in TAMA are a poor prognostic sign, with many patients succumbing to infection.⁴

The pathologic mechanism underlying a GVHD-like reaction in thymomas is complex and not fully elucidated. The major function of the thymus is to educate immature T cells to become immunocompetent, antigen-committed T cells and to develop self-tolerance. This occurs through the deletion of T cells that interact too strongly with self-major histocompatibility complex class I and II molecules. Dysregulation in this selection process and failure to delete T cells bearing T-cell receptors specific for self-proteins are thought to play an important role in the development of autoimmunity and may contribute to the pathogenesis of TAMA.⁴ Additionally, B cells may play a role by generating autoreactive antibodies. This finding is supported by the fact that thymoma-associated myasthenia gravis, resulting from autoantibodies against acetylcholine receptors, improves after thymectomy.⁵ More recently, regulatory T cells have been implicated in TAMA, as they function to maintain peripheral tolerance and inhibit autoimmune responses. Multiple studies have found that a deficiency in

intrathymic and peripheral regulatory T cells has been associated with development of TAMA.⁶

Cutaneous manifestations of TAMA are heterogeneous and may include confluent keratotic papules and scaly erythema, morbilliform eruptions, toxic epidermal necrolysis–like eruptions, or erythroderma.⁷ Other immune-mediated skin diseases, such as vitiligo and alopecia areata, have also been associated with thymomas.⁸

The most common histopathologic findings of GVHD-like erythroderma are parakeratosis, necrotic keratinocytes, and vacuolar interface dermatitis. Recent studies have implicated the role of type I immune responses, specifically type I interferons, in the pathogenesis of interface dermatitis.⁹

The treatment of GVHD-like erythroderma is not well established. Topical and systemic steroids, narrowband ultraviolet B phototherapy, and immunosuppressive drugs have been tried with variable success.⁵ The treatment of the underlying disease in patients with thymomas consists of surgical resection. Complete resection of the thymoma may be the best treatment method for nonmetastatic disease, but many patients who have TAMA may not be good surgical candidates. Because infections commonly lead to death in patients with TAMA,³ systemic immunosuppression should be used cautiously.

To our knowledge, this is the first report in which hydroxychloroquine was used in the treatment of GVHD-like erythroderma. As discussed, the pathogenesis of GVHD is characterized by T-cell dysregulation, hyperactivation of B cells, and likely type I interferon activation. Hydroxychloroquine is thought to impact the generation of type I interferon responses, IgG production, and cytokine production through its effect on lysosomal pH and interference with Toll-like receptor (TLR) signaling (TLR9 and TLR7),¹⁰ which may underlie a positive response of

cutaneous GVHD-like disease to the drug. It should be noted that the therapeutic benefit was seen in combination with IVIg. Hydroxychloroquine acts as an immunomodulator without the risk of infection and could be considered an alternative approach in treating GVHD-like erythroderma in this patient population.

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