

Thymoma-associated multiorgan autoimmunity treated with multimodal therapy including extracorporeal photopheresis



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INTRODUCTION

Patients with malignant thymomas are susceptible to the development of graft-versus-host disease (GVHD)-like disease known as thymoma-associated multiorgan autoimmunity (TAMA). The proposed mechanism of this paraneoplastic phenomenon is a breakdown in the immune regulatory function of the thymus and subsequent activation of T cells. Here, we report a novel case of a patient with TAMA who, following surgical resection and radiation therapy, successfully underwent treatment with a combination of extracorporeal photopheresis (ECP), intravenous immunoglobulin (IVIg), cyclosporine, and prednisone.

CASE REPORT

A 41-year-old woman was admitted to the pulmonary service for progressive shortness of breath and productive cough of 3 months duration. She had a history of myasthenia gravis secondary to thymoma that had previously been resected twice. Her myasthenia gravis was treated with mycophenolate mofetil and pyridostigmine with intermittent prednisone courses, although, during previous exacerbations, she had been treated with IVIg, rituximab, and tacrolimus.

On admission, she reported prior treatment with oral and intravenous antibiotics with minimal relief of her dyspnea and cough. On the third day of admission, a mixed petechial and morbilliform rash involving the extremities with malar erythema developed. A biopsy of the left forearm showed spongiotic and interface dermatitis without

Abbreviations used:

ECP:	extracorporeal photopheresis
GVHD:	graft-versus-host disease
IVIg:	intravenous immunoglobulin
TAMA:	thymoma-associated multiorgan autoimmunity

eosinophilia, favoring a viral exanthem. Within a week, the rash progressed to violaceous scaly and hyperkeratotic plaques of the bilateral acral surfaces (Fig 1, A and B). Repeat biopsy showed vacuolar interface dermatitis with dyskeratosis concerning for drug reaction (Fig 2). Findings of direct immunofluorescence were negative. A computed tomography scan of the chest showed a 2.2-cm pleural-based nodularity along the base of the right lung. Video-assisted thoracoscopic surgery with bronchoscopy revealed a 4.5-cm invasive thymoma in the upper portion of the left lobe. She was discharged on topical steroids with plans to restart her immunosuppressive regimen and planned resection and radiotherapy of the mass.

The rash progressed to desquamative dermatitis interspersed with violaceous macules and papules with necrotic centers. A paraneoplastic process secondary to invasive thymoma was favored, and her rash was most consistent with TAMA. She underwent resection of the thymoma, followed by radiation therapy. She received cyclosporine 85 mg twice a day (later, 120 mg twice a day), pyridostigmine 60 mg 3 times a day, 4 cycles of IVIg, and topical steroids. Despite immunosuppressive therapy, the rash

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Fig 1. Clinical images showing scattered violaceous-to-lichenoid papules coalescing into plaques and blanchable, erythematous desquamating patches on (A) bilateral forearms, palms, and (B) lower portions of the legs and (C) resolution following 2 months of extracorporeal photopheresis.

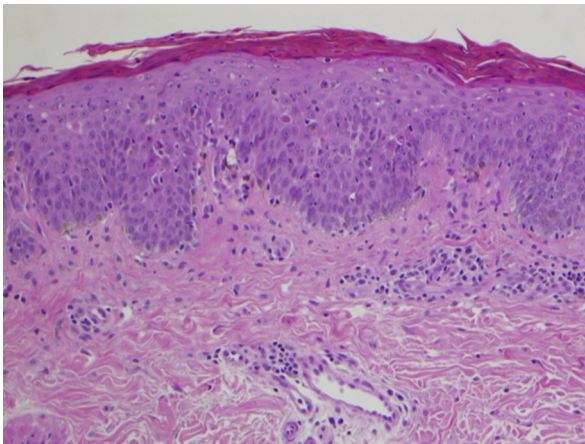


Fig 2. Skin biopsy showing confluent parakeratosis and dyskeratotic keratinocytes in the epidermis, vacuolar alteration in the basal layer, and the presence of perivascular lymphohistiocytic infiltrate with scattered eosinophils in the dermal layer. (Hematoxylin-eosin stain; original magnification: $\times 4$.)

progressed. Thus, we initiated ECP twice a week, and the patient continued cyclosporine, pyridostigmine, IVIg, and topical steroids. Within 2 months of therapy, her rash and symptoms resolved (Fig 1, C). The frequency of ECP was decreased to once weekly for 1 month and then stopped, and the patient was maintained on cyclosporine and prednisone.

DISCUSSION

A normal thymus provides T-lymphocyte precursors an environment in which they undergo development, differentiation, and clonal expansion.¹ The thymus regulates the negative and positive selection of thymocytes. Thymocytes that are

nonreactive toward major histocompatibility complex undergo apoptosis, whereas those that react strongly undergo elimination. This process is impaired in a thymoma, leading to the persistence of activated, autoreactive T cells and subsequent GVHD-like processes, potentially affecting multiple organs. This phenomenon has been termed “TAMA.”^{1,2} To date, there remains no consensus on therapy for TAMA beyond targeting the underlying malignancy. In most cases, patients are treated in a similar manner as GVHD with a combination of corticosteroids and immunosuppressive therapy.

TAMA primarily affects the skin, liver, and intestine. Cutaneous lesions are frequently seen on the face, trunk, and extremities with the involvement of the palms and soles. Skin findings can manifest at variable time points with multiple morphologies.³ Histologic features resemble those of GVHD, including parakeratosis, dyskeratotic keratinocytes, focal liquefaction degeneration of the basal epidermal layer, and lymphocytic infiltration around blood vessels in the papillary dermis. The differential diagnosis for our patient included acute systemic lupus erythematosus, drug eruption including medication-induced connective tissue disease, morbilliform eruption in the setting of systemic infection/viral exanthem, GVHD, and transfusion-associated GVHD.

TAMA is associated with a poor prognosis. Increased mortality due to secondary infections makes immediate, appropriate treatment a priority. To date, reports of topical and systemic steroids, surgical resection, immunosuppressive therapies, radiotherapy, and chemotherapy show limited therapeutic benefits.³⁻⁵ These treatments are likely

ineffective due to the persistence of activated T cells. Although immunosuppressive regimens inhibit this response, they do not induce tolerance. Other treatment modalities that have been reported in the literature include phototherapy. Nakayama et al⁶ reported a case of targeted narrow-band ultraviolet B phototherapy, which improved a localized case of thymoma-associated GVHD-like disease in a 32-year-old Japanese man. Yatsuzuka et al⁷ reported the success of whole-body narrow-band ultraviolet B therapy for the treatment of thymoma-associated GVHD-like disease in a 52-year-old Japanese woman. They discovered that the proportion of FOXP3⁺ cells in the epidermis had increased after phototherapy and posited that increases in T regulatory cells led to tolerance.⁷

Thus, ECP may be a preferred treatment, given its immunomodulatory effects, and an adjuvant therapy as a steroid-sparing modality. It is nonimmunosuppressive, and in GVHD, it is proposed that ECP causes a shift from a helper T cell type 1 to a helper T cell type 2 immune response, thus decreasing cytotoxic T cell stimulation. ECP also increases the production of antiinflammatory cytokines such as interleukin 10 and transforming growth factor β , decreases the levels of proinflammatory cytokines, and stimulates regulatory cells.⁸ The underlying mechanisms seen in TAMA are similar to GVHD; thus, we hypothesize that treatment with ECP targeting these same mechanisms results in disease improvement.

TAMA is a rare condition with a poor prognosis requiring new treatment algorithms. Our case highlights a multipronged treatment regimen with the use of ECP. Understanding the pathophysiology of this phenomenon provides a mechanism for a

targeted approach and makes ECP a logical treatment choice.

Conflicts of interest

None disclosed.

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