Thymoma-associated Graft-versus-Host Disease-like Erythroderma

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We report a 40-year-old woman with recurrent thymoma associated with myasthenia gravis, in whom an unusual form of erythroderma developed. A histological examination revealed a graft-versus-host disease (GVHD)-like reaction. After high-dose steroid therapy, the metastatic thymoma lesion in the abdominal cavity was reduced in size from 9.5 × 6 × 7.5 cm to 4 × 3 × 1 cm in diameter. Nevertheless, the GVHD-like erythroderma become aggravated, her condition worsened, and the patient finally suffered from respiratory failure and died of sepsis. A GVHD-like reaction may be a rare presentation of thymoma-associated immunological disorders such as myasthenia gravis or pure red cell aplasia. Herein, we discuss the present case and review pertinent reports of thymoma cases associated with GVHD.

Key Words: Thymoma, Thymoma-associated immunological disorder, Graft-versus-host disease–like erythroderma.

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Thymomas are frequently associated with autoimmune diseases such as myasthenia. Acute graft-versus-host disease (GVHD), an abnormal immunological condition, occasionally occurs in the setting of bone marrow transplantation after high-dose chemotherapy and transfusion, or transplantation of solid organs containing lymphoid tissue. Herein, we report a patient with recurrent thymoma, in whom GVHD-like erythroderma developed.

CASE REPORT

A 23-year-old woman underwent an extended thymectomy for generalized myasthenia gravis in 1987. A histological examination at the time revealed a thymoma involving the capsule of the tumor, indicating Masaoka stage II disease. The thymoma was classified as type B1 according to the World Health Organization histological classification system.

In 1998, severe general symptoms of myasthenia gravis recurred. Then, recurrence of thymoma was not identified by computed tomography scan when symptoms of myasthenia gravis relapsed. Nevertheless, those symptoms were not relieved by steroid therapy, and immunosuppressive treatment with tacrolimus was introduced in the same year. After beginning tacrolomus therapy, those symptoms were mitigated. In 2002, multiple tumors appeared in the left pleural cavity and were resected. One of those lesions had penetrated the diaphragm; thus, tumor resection was performed along with partial resection of the diaphragm. Two years later, multiple recurrent tumors appeared in the peritoneal cavity. Chemotherapy with carboplatin and paclitaxel was not effective, and thus an ovarian tumor was suspected. Subtotal resection of the peritoneal tumors with bilateral oophorectomy was performed, and a large tumor, 9.5 × 6.0 × 7.4 cm in size, was found behind the liver; it had metastasized from the thymoma. For mass reduction and relief of myasthenia gravis, steroid pulse therapy instead of tacrolimus was started in 2005.

A few days after beginning steroid therapy, erythroderma appeared in the trunk and extremities without other clinical symptoms, and test results were negative for several virus antibodies, except herpes simplex virus 1, which was positive (30.1) before beginning therapy. Further, no bacteria were found in the epidermis, and the patient did not have any lesions specific to Stevens–Johnson syndrome, so this disorder was ruled out. In addition, a histological examination of a biopsy specimen from the skin revealed parakeratosis in the epidermal layer, with a number of apoptotic bodies accompanied by lymphocytic infiltration, suggesting the development of acute, GVHD-like reaction (Figure 1). Immunohistochemical staining also revealed that the infiltrated T cells were predominantly $CD8^+$, whereas keratinocytes expressing $HLA\text{-}DR^+$ and $CD1a^+$ were occasionally intermingled. The clinical course and histological and immunohistochemical findings justified the diagnosis of GVHD-like erythroderma. Although high-dose oral steroid therapy, combined

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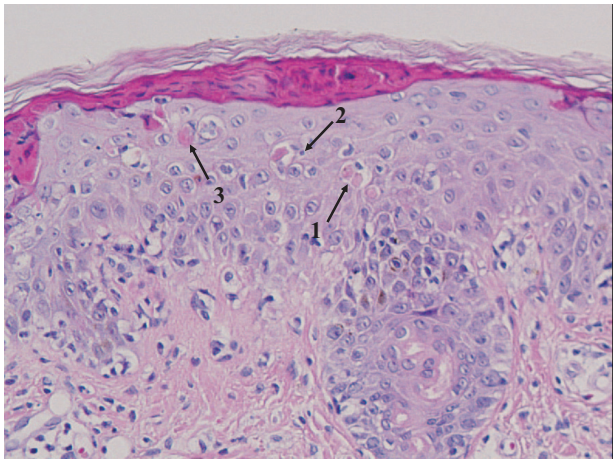

FIGURE 1. Histopathological examination findings revealed perivascular lymphocytic infiltration in the dermis (*arrow 1*), as well as parakeratosis (*arrow 2*), apoptosis, and satellite cell necrosis (*arrow 3*) in the epidermis. Hematoxylin and eosin stain (weak magnification).

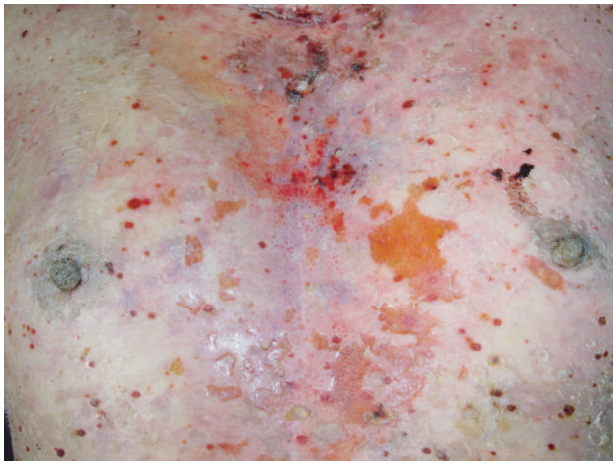

FIGURE 2. Keratotic erythroderma, vesicles, and ulcers in the skin. (The picture was colored.)

with immunosuppressive therapy with cyclosporine A, was given, the condition was not resolved. During the high-dose steroid therapy, erythroderma with vesicles and ulcers appeared (Figure 2); this may have been caused by the herpes simplex infection, because the skin had phlyctenula with deep red areolas like varicella, as in aposi's varicelliform eruption. Nevertheless, the other virus antibodies remained negative, and the other skin lesions could not have occurred from herpes simplex 1 alone. Therefore, we continued therapy against GVHD-like reaction. Interestingly, the abdominal tumor was remarkable reduced in size along with the intensified acute GVHD-like reaction, whereas the erythroderma became more severe. Erythroderma was mitigated 2 months after beginning the therapy. Weaning of steroid was intended, but the erythroderma appeared again, and myasthenic crisis also developed. Tracheal intubation was performed, and artificial respiration was started. Finally, the patient suffered from respiratory failure and died of sepsis 5 months after the appearance of the erythroderma. An autopsy was subsequently performed.

Histologically, hyperkeratosis and parakeratosis with spongiotic change and apoptotic cells were found over the epidermal layer. In addition, a bandlike infiltration, exocytosis of lymphocytes, and dense, perivascular, lymphocytic infiltrations were observed at the dermoepidermal junction (Figure 3). Immunohistochemical staining revealed that the lymphocytes infiltrating the epidermis were predominantly $CD8^+$ T cells accompanied by a few $CD4^+$ T cells. The tumor was present on the liver and was sized $4 \times 3 \times 1$ cm, with histological results showing it to be a type B2 thymoma. A thorough histological examination did not reveal a GVHD-like reaction in other organs. These findings confirmed the diagnosis of GVHD-like erythroderma, which developed during treatment for recurrent thymoma.

DISCUSSION

Thymomas are well known for their frequent association with paraneoplastic autoimmune diseases, including myasthenia gravis, pure red cell aplasia, and acquired hypogammaglobulinemia. Nevertheless, the mechanism for the development of several autoimmune disorders associated with thymomas has not been fully elucidated. Several studies have suggested the possible role of neoplastic epithelial cells present in the thymoma for induction of autoreactive T cells. Further, $CD4^+CD8^+$ T cells, the typical phenotype of normal cortical thymocytes, are abundant in thymic tissue, indicating that neoplastic epithelial cells in the tumor are able to retain the function of the thymic cortex for induction of T cell development. On the other hand, the expression level of HLA-DR molecules in thymoma cells is decreased compared with that of normal thymic epithelial cells. In addition, a normal thymic structure, in which autoreactive T cells are considered eliminated, might be absent in thymoma tissues. These observations have led to the notion that alternated T cell development and selection in thymomas might be responsible for the development of autoimmunity.

GVHD is an abnormal immunological condition caused by the activation of donor T cells that show clonal expansion after transfusion or bone marrow transplantation.[1] The present patient did not have a history of transplantation. Further, all transfused blood was pretreated with radiation, which is considered to prevent GVHD. Thus, exogenous causes for GVHD-like symptoms in this patient seem to be unlikely, and a drug-induced allergy or infection could also be ruled out by the medication history and laboratory data.

Several cases of GVHD-like reaction associated with a thymoma have been reported (Table 1).[2–7] The findings in those reports, together with those of the present case, suggest that autoreactive T cells derived from thymomas play a role in the development of GVHD-like reactions.

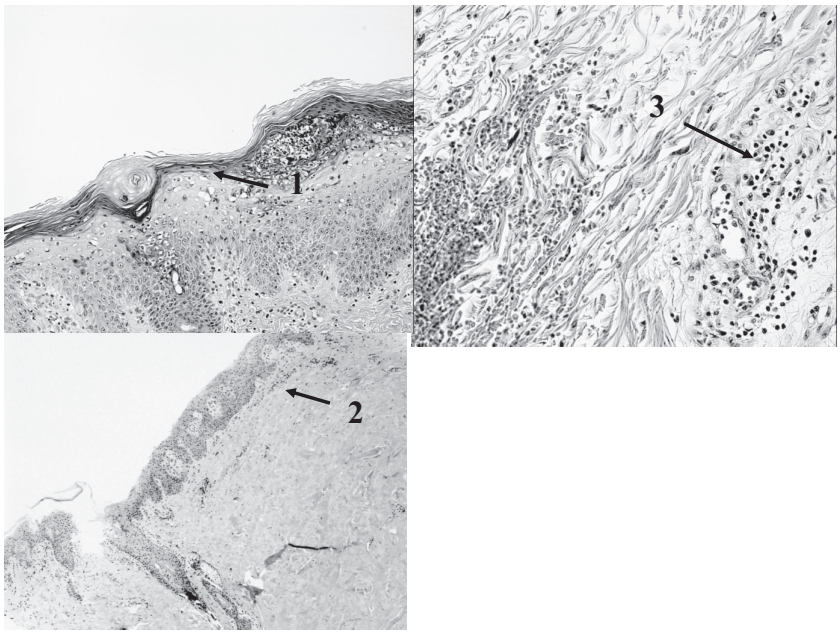

FIGURE 3. Hyperkeratosis and parakeratosis (*arrow 1*) in the epidermal layer with a number of spongiotic and dyskeratotic cells. Bandlike infiltration and exocytosis of lymphocytes (*arrow 2*), along with perivascular, lymphocytic infiltration (*arrow 3*), can be seen at the dermoepidermal junction.

TABLE 1. Reported Cases of Graft-versus-Host Disease–like Reaction in Association with Thymoma

Case	Age/Gender	Symptom	Complication	Outcome
1, (2)	57/female	Diarrhea Erythema multiforme Jaundice	Hypo-gGlb	Died
2, (3)	38/female	Maculoerythematous rash Liver dysfunction Diarrhea	MG	Died
3, (4)	47/male	Maculoerythematous rash Diarrhea	Hypo-gGlb PRCA	Alive (7 mo)
4, (5)	46/female	Erythroderma desquamatuva	None	Died (8 mo)
5, (6)	46/male	Diarrhea	None	Alive
6, (7)	20/male	Diarrhea	None	Alive (2 yr)

The reference number is listed next to the case number in parentheses. Hypo-gGlb, hypogammaglobulinemia; MG, myasthenia gravis; PRCA, pure red cell aplasia.

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