Unusual association of diseases/symptoms

Chemotherapy improves thymoma-associated graft-versus-host-disease-like erythroderma

Tatsuya Nagano,¹ Yoshikazu Kotani,¹ Kazuyuki Kobayashi,¹ Nanako Tomita,¹ Kyosuke Nakata,¹ Akihiro Sakashita,¹ Yasuhiro Funada,¹ Hiroshi Nagai,² Tomoo Itoh,³ Yoshihiro Nishimura¹

¹Division of Respiratory Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan;

²Division of Dermatology, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan;

³Department of Diagnostic Pathology, Kobe University Graduate School of Medicine, Kobe, Japan

Correspondence to Dr Kazuyuki Kobayashi, kkoba@med.kobe-u.ac.jp

Summary

Graft-versus-host-disease (GVHD) with erythroderma can rarely occur in the context of thymoma and is associated with a poor prognosis due to an increased risk of infection-related death. The present study describes a case of a 50-year-old man with malignant thymoma who developed sepsis in addition to skin manifestations similar to that seen in GVHD. This patient experienced marked improvement in skin lesions in response to steroids and combination chemotherapy with carboplatin and paclitaxel, with subsequent resolution of infection. The present study describes the clinical course of this patient, followed by a review of pertinent reports of thymoma associated with GVHD with particular focus on the efficacy of treatment strategies.

BACKGROUND

Graft-versus-host disease (GVHD)-like disorders can occur in the context of thymoma, albeit rarely. These GVHD-like disorders manifest with skin, liver and intestinal involvement in a manner that is similar to that seen with typical GVHD induced after blood transfusion or solid-organ transplantation and are usually distinguished from other autoimmune conditions associated with thymoma such as myasthenia gravis, pure red cell aplasia and hypogammaglobulinaemia.^{1–2} This thymoma-associated GVHD-like disorder is thought to be partly because thymoma retains the function of induction of T cell development and lacks normal thymic structure, in which autoreactive T cells are considered eliminated.³ Review of the literature identified seven cases of thymoma associated with GVHD-like skin lesions.^{3–9} All patients who did not undergo complete resection of the thymoma developed severe infections, leading to death in the majority of cases. These observations underscore the need for effective treatments for GVHD-like erythroderma in patients with unresectable thymoma.

The current study describes a case of thymoma-associated GVHD-like erythroderma that was successfully treated with corticosteroids and chemotherapy. The case presentation is followed by a review of pertinent reports of thymoma associated with GVHD, focusing on the efficacy of treatment strategies.

CASE PRESENTATION

A 50-year-old man was admitted to our hospital in March 2010 because of erythroderma affecting his face, trunk and upper and lower extremities. Seven years before admission, he had suffered from dysphagia and upper extremity weakness and was diagnosed with thymoma

with myasthenia gravis. The thymoma was characterised as stage IVa according to the classification proposed by Masaoka *et al*¹⁰ and as type AB according to the WHO histological classification system (figure 1A). He underwent extended thymectomy in 2003, but the tumour could not be completely resected. Postoperatively, he had repeated exacerbations of myasthenia gravis, which required mechanical ventilation and intensive steroid therapy. Ultimately, maintenance suppression therapy for myasthenia gravis was instituted with corticosteroids, tacrolimus and the cholinesterase inhibitor pyridostigmine. Three years later (between July and August, 2006), the thymoma was treated with 50.4 Gy of thoracic radiation therapy, but the tumour gradually enlarged.

Two months before admission, erythematous and scaly plaque appeared on the patient's face, trunk and upper and lower extremities (figure 1B).

INVESTIGATIONS

On admission, the patient was afebrile. Physical examination revealed diffuse erythematous plaques and oedema on the lower extremities but did not reveal jaundice or abdominal or neurological abnormalities. CT scan of the chest showed tumours in the mediastinum (figure 2A) and right pleura (figure 2B). Laboratory testing showed elevated serum levels of alanine aminotransferase (43 IU/l), lactic dehydrogenase (510 IU/l), γ -glutamyl transpeptidase (144 IU/l), C reactive protein (3.77 mg/dl) and acetylcholine receptor antibody (15.5 mmol/l) as well as decreased serum levels of total protein (6.1 g/dl) and albumin (2.9 g/dl). Complete blood count testing revealed an increased number of white blood cells (25 200 / μ l) and slightly reduced haemoglobin (13.0 g/dl). Serum levels of immunoglobulin A, G and M were within normal limits.

Figure 1 Microscopic findings of the thymoma tissue (A) and skin lesion (C) with H&E staining and macroscopic picture of the skin (B, D). The thymoma is composed of neoplastic thymic epithelial cells that have a spindle or oval shape, lack nuclear atypia with scant lymphocytes (left side, WHO type A), and are admixed with foci rich in non-neoplastic lymphocytes (right side, WHO type B), and finally classified as Type AB ($\times 200$) (A). Skin specimen revealed parakeratosis and hyperkeratosis in the epidermal layer, liquefaction degeneration and Civatte bodies, and lymphocytic infiltration around the blood vessels in the superficial dermis (low-power field) (C). Oedematous erythema accompanied by scale formation was found in trunk before treatment (B), with marked improvement occurring after chemotherapy (D).

Figure 2 CT of the chest revealed a mediastinal mass (A) and nodules located in right pleura (B) at the time of admission.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for this rash included drug eruption, viral infection and transfusion-associated GVHD. A drug-induced allergy was excluded based on his medication history. Furthermore, he had not received any blood transfusions or solid-organ transplantation before onset of these skin lesions, nor was there any indication of infection with HIV or cytomegalovirus. A skin biopsy was performed, and histopathological examination revealed

a GVHD-like reaction consisting of hyperkeratosis and parakeratosis in the epidermal layer with liquefaction degeneration and numerous Civatte bodies, which represent apoptotic keratinocytes accompanied by lymphocytic infiltration around the blood vessels in the superficial dermis (figure 1C). Based on his history, clinical examination and histopathology, the eruption was thought to be most consistent with thymoma-associated GVHD-like erythroderma.

TREATMENT

Three cycles of chemotherapy with carboplatin (area under the curve of 6561 mg) and paclitaxel (200 mg/m², 362 mg) was administered. He developed neutropenic fever on day 8 of the first cycle of chemotherapy and received cefotaxime and arbekacin. The fever remitted, and a second course of chemotherapy was administered. On day 1 of the second course of chemotherapy, the patient developed diarrhoea and fever, but use of meropenem and then ciprofloxacin resulted in resolution of symptoms and fever. Stool specimen was negative for the enteric pathogens and for *Clostridium difficile* toxin, but *Campylobacter* species were identified in blood cultures obtained during onset of fever on day 1.

OUTCOME AND FOLLOW-UP

Evaluation after two cycles of chemotherapy showed marked improvement in erythroderma (figure 1D). A CT scan performed at the end of the second cycle of chemotherapy showed a 14.2% reduction of tumour volume. Chemotherapy was terminated after the third cycle due to the development of grade 3 neuropathy, as assessed by the Common Terminology Criteria for Adverse Events Version 3.0 grading system proposed by the National Cancer Institute.

After three cycles of chemotherapy, moderate erythroderma recurred, and treatment with intensive steroid therapy (1 g of methylprednisolone on three consecutive days) was instituted. Erythrodermic manifestations improved, and neuropathic symptoms were controlled with long-acting oxycodone and gabapentin. Unfortunately, the patient experienced recurrent worsening of erythroderma and onset of peripheral oedema. Intensive steroid therapy was

again initiated followed by chemotherapy with cisplatin (50 mg/m², 92.5 mg), doxorubicin (40 mg/m², 74.0 mg), vincristine (0.6 mg/m², 1.11 mg) and cyclophosphamide (700 mg/m², 1295 mg). This resulted in improvements in skin lesions and oedema, with similar degrees of improvement in response to each mode of therapy (ie, steroids and chemotherapy). However, worsening neuropathy led to discontinuation to platinum-based agents. On follow-up at 11 months after the last course of chemotherapy, he is still alive.

DISCUSSION

Unresectable thymoma with GVHD-like erythroderma is associated with a poor prognosis, mainly related to the increased risk of (sometimes fatal) infection.¹¹ Prior to the present study, there were no reports of patients with unresectable thymoma-associated GVHD-like erythroderma who were successfully treated with chemotherapy.

Table 1 summarises all of the cases of thymoma-associated GVHD that have been reported in the literature.^{3–9 12 13} These studies reveal that treatment with high-dose corticosteroid therapy is effective for GVHD but can also increase the risk of infection due systemic immunosuppression and other steroid-related adverse effects.¹⁴ In addition, erythroderma secondary to malignancy is typically persistent and refractory to steroid therapy.¹⁵ Indeed, almost all the patients with unresectable thymoma who developed GVHD-like skin lesion after experiencing improvement of corticosteroids ultimately died due to severe infection.^{3 6–9} By contrast, patients who underwent complete resection of thymoma achieved relapse-free survival.^{4 12} These results suggest that steroid therapy and antineoplastic therapy are needed to maintain improvements seen in response to

Table 1 Efficacy of treatments for thymoma-associated graft-versus-host-disease

	GVHD with skin lesions			GVHD without skin lesions
	Complete resection	Chemotherapy	Others	Complete resection or BMT
Number of patients	1	1	6	2
Age				
Median, years	47	50	46	33
Range			38–57	20–46
Gender				
Male	1 (100%)	1 (100%)	1 (17%)	2 (100%)
Female	0	0	5 (83%)	0
Complicating paraneoplastic syndrome	1 (100%)	1 (100%)	5 (83%)	NA
Complicating infection	1 (100%)	1 (100%)	6 (100%)	NA
Responder/non-responder ratio*				
Systemic corticosteroids	0/1	1/0	4/1	1/0
Surgery	1/0			0/1
Chemotherapy		1/0†		1/0‡
Radiation			1/0	
Topical triamcinolone			1/0	
Bone marrow transplantation				1/0
Survivals§				
Median, months	18	13	8	NA
Range			5–12	
Outcome	Achieved relapse-free survival	Alive	Died of infection (83%) Died of complications (17%)	Achieved relapse-free survival

*Response to treatment for GVHD.

†Treated by chemotherapy with carboplatin and paclitaxel.

‡Treated by chemotherapy with cisplatin, doxorubicin, vincristine and cyclophosphamide.

§After the appearance of graft-versus-host-disease like skin lesion.

BMT, bone marrow transplantation; GVHD, graft-versus-host-disease; NA, not available.

initial steroid therapy. Indeed, the use of this combination therapy may account for the favourable outcome seen in the present case.

In the current case, the patient was given chemotherapy with carboplatin and paclitaxel and later, chemotherapy with cisplatin, doxorubicin, vincristine and cyclophosphamide. Agents with good activity against thymoma include cisplatin, vincristine, doxorubicin, etoposide, cyclophosphamide and ifosfamide.¹⁶ Therapy with corticosteroids is also effective for the treatment of metastatic thymoma.¹⁷ Other reports have shown good antithymoma activity with a combination of carboplatin and paclitaxel.^{18 19} However, because of the relatively small number of patients with advanced thymoma, the efficacy of chemotherapy has not been studied in a comprehensive manner. Therefore, the standard of care for the treatment of invasive thymoma remains unclear.

Of note, use of a central venous catheter for delivery of chemotherapeutics or other agents can be associated with a high risk of infection in patients with GVHD-related erythroderma due to inflamed, fissured and excoriated skin, and the related risk of bacterial colonisation.¹⁵ In some cases, this can result in sepsis. In the present case, we utilised carboplatin and paclitaxel because of the relatively short intravenous infusion time and because these agents do not require excessive intravenous hydration. Similarly, when we administered antibiotics, we selected drugs with longer half-lives that did not require frequent administration.

Learning points

- ▶ Unresectable thymoma with GVHD-like erythroderma is associated with a poor prognosis, mainly related to the increased risk of infection.
- ▶ High-dose corticosteroid therapy is effective for GVHD but can also increase the risk of infection.
- ▶ Chemotherapy in combination with steroids and antibiotics was effective, well tolerated, and resulted in good outcomes when used for treatment of thymoma-associated GVHD-like erythroderma in a patient who could not otherwise undergo complete resection of thymoma.

Competing interests None.

Patient consent Obtained.

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Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Nagano T, Kotani Y, Kobayashi K, Tomita N, Nakata K, Sakashita A, Funada Y, Nagai H, Itoh T, Nishimura Y. Chemotherapy improves thymoma-associated graft-versus-host-disease-like erythroderma. *BMJ Case Reports* 2011;**10**:1136/bcr.03.2011.3936, date of publication

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