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SHORT COMMUNICATION

Cutaneous Manifestations of Thymoma-associated Multi-organ Autoimmunity: A Fatal Sign

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Association of thymoma and cutaneous autoimmune disorder has been reported previously. Paraneoplastic pemphigus (PNP) and lichen planus (LP) have been commonly reported as cutaneous complications of thymoma (1, 2). Thymoma-associated multi-organ autoimmunity (TAMA) is a rare paraneoplastic disease that presents manifestations resembling graft-versus-host disease (GVHD) in thymoma. TAMA tends to have an unfavourable prognosis, due to complications of infectious diseases (3, 4). Of the several case reports of TAMA, 4 in the English literature were without extracutaneous GVHD-like manifestations (3, 5–7). Of these, only one case with a fatal outcome has been described (7). We describe here the first case of TAMA developing GVHD-like manifestation solely in the skin, who died of progressive multifocal leukoencephalopathy (PML) one year after being diagnosed with TAMA.

CASE REPORT

A 55-year-old Japanese woman who had been diagnosed with thymoma (WHO TypeB3, Masaoka stage IVA) 5 years earlier presented with a 2-week history of eruptions on the whole body. Her medical history included pure red cell aplasia 3 years earlier, which remitted with cyclosporine and required no further treatment. Physical examination revealed numerous fresh-red keratotic papules that tended to coalesce into scaly plaques on the face, trunk and extremities (Fig. 1A). No mucosal eruptions were observed. She had no gastrointestinal symptoms. There was no history of potentially eruption-inducing drugs. Routine laboratory tests showed no abnormalities in liver enzymes. Zinc deficiency was excluded by blood tests. No infection of Treponema pallidum, hepatitis virus B, hepatitis virus C, human immunodeficiency virus or human T-cell lymphoma/leukaemia virus type 1 was found. Collagen diseases were ruled out based on the negative serum autoantibody results.

The histopathology of a keratotic papule showed psoriasiform epidermal hyperplasia and parakeratosis in the stratum corneum, necrotic keratinocytes, exocytosis and liquefaction degeneration in the epidermis, and the infiltration of lymphocytes in the dermis (Fig. 1B). Immunohistochemical findings demonstrated infiltration of $CD3^+$ T cells in the epidermis and more $CD8^+$ than $CD4^+$ T cells (Fig. 1C). A marked decrease in $CD1a^+$ Langerhans cells in the epidermis was observed (Fig. 1D). Indirect immunofluorescence (IIF) on normal human skin was negative in the intercellular spaces of the epidermis and the dermal–epidermal junction (data not shown). The histopathological, immunohistochemical and IIF findings were suggestive of GVHD; however, GVHD was ruled out because the patient had never received hematopoietic stem cell transplantation. Based on the clinicopathological findings and IIF results, a final diagnosis of TAMA was made.

Although she had received repeated chemotherapy for thymoma previously and had refused further chemotherapy at this time, she hoped for improvement of the skin lesions. We administered 0.6 mg/kg/day of oral prednisolone, and the eruptions gradually improved, leaving post-inflammatory pigmentation (Fig. 1E). We tapered this to 0.2 mg/kg/day of prednisolone, but the eruptions recurred and became erythroderma. Eruption severity inversely corresponded to the dose of prednisolone. During the course we tried to use cyclosporine for the skin lesion, but it was not effective and we immediately discontinued. A year after the diagnosis of TAMA, she died of PML, which had been confirmed by detection of JC virus (John Cunningham virus) by PCR in her cerebrospinal fluid. Autopsy revealed that metastasis of the

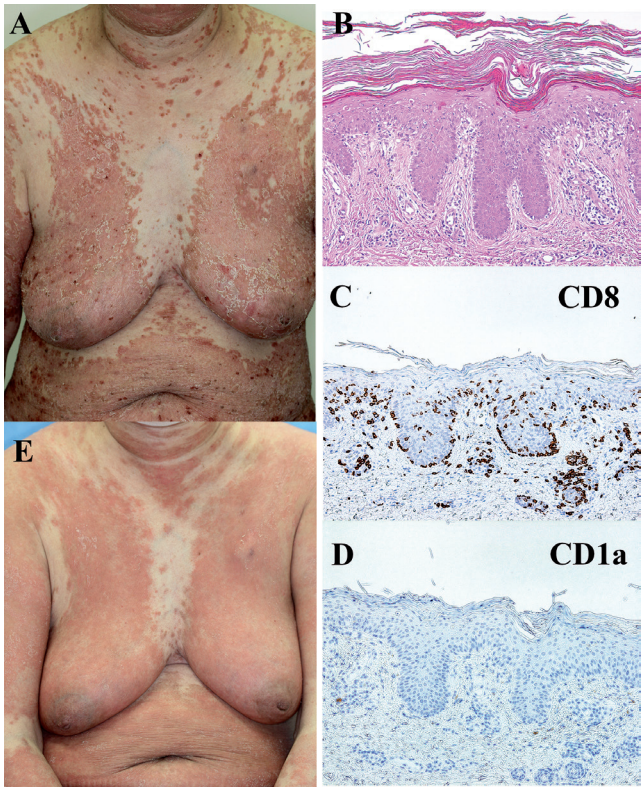

Fig. 1. (A) Red keratotic papules tended to coalesce into plaques on the trunk. (B) Histopathology shows parakeratosis in the stratum corneum, psoriasiform epidermal hyperplasia, necrotic keratinocytes, exocytosis and liquefaction degeneration in the epidermis and infiltration of lymphocytes in the dermis, all of which are suggestive of graft-versus-host disease (haematoxylin and eosin stain, original magnification ×100). Immunohistochemistry study shows (C) significant infiltration of lymphocytes positive for CD8 and (D) the absence of $CD1a^+$ Langerhans cells, suggesting that the infiltration was due to autoreactive T cells and not metastasis of the thymoma (original magnification ×100). (E) The eruptions improved, leaving pigmentation after 10 weeks of oral prednisolone.

thymoma was not proven and that the tumour size had been properly controlled by the previous chemotherapy. Demyelination was observed in the respiratory centre of the medulla oblongata by Kluever-Barrera staining.

DISCUSSION

TAMA is a rare paraneoplastic disease defined as thymoma with liver, intestine or skin manifestations (4). The first case of TAMA, described by Kornacki et al. (8) in 1995, presented as GVHD-like colitis in a patient with thymoma. Typical eruptions of TAMA include confluent keratotic papules and scaly plaques, morbilliform eruptions, erythroderma and mucosal erosions (4, 9, 10). Four cases of TAMA without extracutaneous GVHD-like manifestations have been reported (3, 5–7). The diagnoses were made based on the identical clinical and histopathological findings. Differential diagnoses include lichenoid drug eruptions, viral infections, lichen planus, pityriasis rosea, pityriasis lichenoides chronica, PNP, acrodermatitis enteropathica, persistent pruritic eruption of adult-onset Still disease, GVHD and transfusion-associated GVHD (4, 7, 10). Immunohistochemically, infiltration of $CD8^+$ T cells, a low CD4:CD8 ratio and a marked decrease in $CD1a^+$ Langerhans cells in the epidermis are useful in diagnosing TAMA, since similar findings are characteristically observed in GVHD (3, 5, 11). Our case showed typical findings of TAMA in clinical appearance, histopathology and immunohistochemistry.

Two main theories for the mechanism responsible for the development of GVHD-like reaction in thymoma have been hypothesized. One is that dysfunction in the deletion of autoreactive T cells in thymoma without *AIRE* expression might induce infiltration of autoreactive $CD8^+$ cytotoxic T cells (CTL) to the epidermis (12). The other is that insufficiency in $Foxp3^+$ regulatory T cells in the skin might cause autoreactive CTL invasion into the epidermis, which might result in cutaneous GVHD-like reactions (3). In our case, invasive $CD8^+$ T cells in the epidermis were positive for cytotoxic enzymes or cytokines of perforin, granzyme B- and T-cell restricted intracellular antigen-1 (data not shown), which in part supports both hypotheses.

There is no consensus on treatments for TAMA. Surgical resection, chemotherapies for thymoma, oral corticosteroids or immunosuppressive medications may be effective (4, 6, 10). In our case, the correspondence between prednisolone dose and skin symptom severity was consistent with the typical course of TAMA. Although cyclosporine was used in previous case reports of TAMA with cutaneous manifestations, the effect depends on the cases (3, 7). The eruption of our patient did not correspond to cyclosporine. The prognosis of patients with TAMA is reported to be unfavourable due to an increased risk of infection-related death (4, 9, 10). Furthermore, prednisolone has to be used in the majority of cases because of the severe generalized skin manifestations, even if the patient presents with only cutaneous lesions. Murata et al. (7) reported a case of TAMA treated with high-dose prednisolone (2 mg/kg/day), followed by fatal aspergillosis. We report the first case of TAMA without extracutaneous GVHD-like manifestations who died of PML.

In conclusion, dermatologists should pay attention to complications with opportunistic infections even in patients with TAMA who present only cutaneous lesions while administering immunosuppressive therapies.

The authors declare no conflicts of interest.

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