INTRODUCTION

The incidence of dermatomyositis (DM) is reported to be approximately 1/100,000. The majority of cases are idiopathic. However, in approximately 15% to 30% of adult-onset DM cases, DM represents a paraneoplastic syndrome caused by an underlying malignancy [1,2]. The immune mechanisms involved in DM are underdetermined, but are supported by the presence of T cells, macrophages, and dendritic cells in muscle tissue. T cells may have direct and indirect toxic effects on muscle fibers, causing muscle fiber necrosis and muscle weakness, but the target of the immune reaction is unknown [3].

Exanthematous drug eruptions are the most common form of drug-induced cutaneous eruptions. These reactions begin 4 to 21 days after the culprit drug is administered and rapidly evolve into widespread rashes, while recurrence after rechallenge begins within 2 days. This onset pattern suggests that rather than direct toxicity, sensitization and specific immunological memory occur when a dose-related threshold is reached. Resolution after drug discontinuation (known as “dechallenge”) also helps identify the causative agent [4,5]. Management includes discontinuation of the culprit drug and antipruritic therapy. The spectrum of medications reported to cause drug-induced exanthema is wide and includes drugs of multiple classes, most commonly antibiotics.

Our patient presented with DM as a paraneoplastic syndrome associated with metastatic breast cancer. Two years later, she experienced an exanthematous drug eruption that was related to paclitaxel-based palliative chemotherapy.

Here, we describe a patient with metastatic breast cancer who developed paraneoplastic DM and a paclitaxel-induced exanthematous drug eruption. This case report emphasizes the importance of evaluating internal malignancies, such as advanced breast cancer, in newly developed DM patients. In addition, it presents a rare case of paclitaxel-induced exanthematous drug eruption. The purpose of this case report highlights the immunological pathogenic mechanism of DM and drug eruption in underlying advanced breast cancer.

Key Words: Breast neoplasms, Dermatomyositis, Drug eruptions, Immunity, Paclitaxel

CASE REPORT

In May 2011, a 55-year-old postmenopausal woman presented to a community hospital for the evaluation of polyarthralgia and erythematous skin rashes with itching sensation. She was a never smoker and not an alcoholic, and had a history of situs inversus totalis diagnosed at the age of 33 years. The...
rash was initially diagnosed as rheumatic dermatitis and treated with oral steroids and antihistamines with slight improvement. At that time, her physician in charge coincidentally noticed a palpable nodule in the left breast. A diagnostic core needle biopsy revealed invasive ductal carcinoma in the left breast (Figure 1A). The tumor was negative for estrogen and progesterone receptors. HER2/neu expression was immunohistochemically positive (Figure 1B). A computed tomography scan of the chest, abdomen, and pelvis and a bone scan showed multiple lymph node metastases (Figure 2). She was

Figure 1. A diagnostic core needle biopsy for carcinoma in the left breast. (A) H&E stain revealed invasive ductal (×200). (B) HER2/neu expression was positive by immunohistochemistry (×200).

Figure 2. Radiologic findings for chest computed tomography (CT). CT scan shows the primary breast cancer of the left breast (A) and multiple lymphadenopathies of the left axilla (B), mediastinum (C, D), right axilla (E), and paratrachea (F). Arrows indicate enlarged lymph nodes and mass.
referred to our breast clinic for further oncologic evaluation and care. In our clinic, she was diagnosed with DM accompanying cutaneous erythematous eruptions, heliotropic rashes over both upper eyelids, Gottron's papules on both elbows, and progressive weakness/arthritis of the upper and lower limbs. The patient's complete blood cell count and differential, urinalysis, electrolytes, hepatitis serology, myoglobin, anti-Jo-1 antibody, extractable nuclear antigen I (ENA I) antibody, ENA II antibody, and anti-cyclic citrullinated peptide antibody were within the normal range.

Alanine transaminase and lactate dehydrogenase levels were elevated (83 U/L and 1,560 IU/L, respectively). Anti-nuclear antibody was weakly positive (1:40). The skin biopsy specimen taken from the left hip showed perivascular lymphocyte and neutrophil infiltration with small, dark nuclei and scant cytoplasm, which was consistent with DM (Figure 3). Since the above test results were consistent with probable DM according to diagnostic criteria [6], a muscle biopsy and electromyogram were not performed.

The patient was treated with systemic steroid therapy with good control of joint pain and weakness as well as partial remission of skin rashes. The breast cancer was at stage IIIC (cT1N3M0) as assessed using the American Joint Committee on Cancer classification. She received palliative chemotherapy for 2 years as part of the clinical trial MARRIANE study (T-DM1 and pertuzumab). She tolerated the breast cancer therapy well, with all manifestations of DM resolving after chemotherapy. After the completion of 37 sessions of palliative chemotherapy, the tumor showed further progression. Skin manifestations of DM occasionally recur in association with significant stressors, but she experienced no recurrence of symptoms suggestive of myositis after chemotherapy. She subsequently received second-line taxane-based chemotherapy with paclitaxel 175 mg/m² IV over 24 hours and trastuzumab 4 mg/kg, every 3 weeks. Nine days after the first-cycle infusion, multiple erythematous maculopapular rashes developed on the whole body symmetrically sparing the palms and soles (Figure 4A). Routine blood tests demonstrated anemia and eosinophilia (hemoglobin 10.8 g/dL, absolute lymphocyte count 1,116 × 10³/μL, neutrophil count 12.0 × 10³/μL, platelet count 189 × 10³/μL). Her vital signs were normal (blood pressure, 110/68 mm Hg; heart rate, 110/min; and temperature, 36.7°C). There was no sign of infection. There was no mucous membrane involvement (ocular, oral, or genital lesions) or nail change. She had not taken any medications. The patient was treated with supportive management, especially systemic steroids and antihistaminics, and the skin rashes gradually resolved over 1 week. She subsequently received paclitaxel 80 mg/m² per week. However, 5 minutes after her second-cycle infusion of paclitaxel at reduced doses, she complained of skin rashes with itching sensation on the whole body (Figure 4B). Immediately after the cessation of paclitaxel infusion, she was

Figure 3. Microscopic findings for skin biopsy. (A) Perivascular and interstitial lymphocytic infiltration with small, dark nuclei and scant cytoplasm, are compatible with dermatomyositis (H&E stain, × 400). (B) Aggregates of mature lymphocytes are seen surrounding vessels (H&E stain, × 200).
treated with systemic steroids and antihistamines. Her cutaneous lesions improved, and paclitaxel therapy was then stopped after two cycles. Since she was receiving no other medication, associations between exanthema and paclitaxel were suggested by the complete resolution of the skin lesions within weeks of drug withdrawal. The clinical features were consistent with a drug-induced morbilli-form exanthema, and critical assessment disclosed circumstantial evidence to implicate paclitaxel as the cause of this complication [4,5]. Thus, after first- and second-cycle chemotherapy, her skin rashes were diagnosed as paclitaxel-induced exanthema. The exanthematous drug eruption did not recur after paclitaxel discontinuation. At that time, doxorubicin chemotherapy was planned, and the patient continued to have regular follow-up.

**DISCUSSION**

Autoimmune diseases may develop in patients with malignancies through diverse mechanisms. They may occasionally be associated with serious clinical entities. The emergence of these entities may be attributed to autoantibodies generation, paraneoplastic syndromes, direct invasion of the joints and muscles by tumor cells, or combination chemotherapy [7]. With significant advances in immunomodulatory therapies for cancer and autoimmune disease numerous investigators have attempted to understand the role of the human immune system in cancer and autoimmune disease [8].

After a cutaneous presentation of DM associated with metastatic breast cancer, our patient experienced a cutaneous exanthematous drug eruption to paclitaxel. The exact pathogenetic mechanisms of DM and adverse drug reactions have not been determined. However, it is speculated that there is a possible biological association between DM and malignancy. It has been suggested that a common environmental factor may simultaneously act as a trigger of inflammation and as a carcinogen. Some investigators have implicated an antitumoral immune reaction that evolves into an autoimmune syndrome through interactions between muscle and skin antigens [9].

Paclitaxel, which is thought to have caused the drug eruption in this case, is an antineoplastic agent for various malignancies. Major adverse reactions include peripheral neuropathy, myelotoxicity, bradycardia and hypotension, alopecia,
nausea and emesis, arthralgia and myalgia, granulocytopenia, and hypersensitivity [10]. However, there have been few cases of exanthematous drug eruption to paclitaxel in the literature. Clinicians have suspected for years that drug reactions are mediated by immune mechanisms because their occurrence suggests sensitization and specific immunological memory rather than direct toxicity [11]. It is possible that granulysin is expressed at different levels in multiple cutaneous adverse drug reactions and that skin-infiltrating CD8+ T and NKp46+ cells are prominent sources of granulysin [7,12].

A strong relationship between autoimmune immunological pathogenesis and underlying malignancy has been demonstrated in the literature [8,9]. Numerous observations suggest that the immune system inhibits cancer progression. For example, when patients are on long-term immunosuppressive medications, for example cyclosporine for the prevention of graft-versus-host disease after organ transplantation, the odds of cancer development is increased. Patients who are immunocompromised by human immunodeficiency virus infection are more susceptible to certain malignancies, including acquired immunodeficiency syndrome-defining cancers such as Kaposi sarcoma and central nervous system lymphomas as well as lung cancer and Hodgkin lymphoma. In addition, similar to the introduction a novel virus into a population, cancer in transplanted organs may develop rapidly in recipients even though malignancies were unapparent or in remission in the donor.

On a cellular level, T-cells in the tumor environment contribute to antitumor immune activity by interacting with antigen-presenting molecules displaying tumor-associated antigens (TAA), antigenic proteins expressed by a tumor that are unique, and with mutated or even normal self-proteins with upregulated expression. In response to interactions with TAA, tumor-infiltrating lymphocytes (TIL) may produce effector molecules, including granzymes, perforins, cytokines, and interferon γ that are directly cytotoxic to tumor cells. In a few studies, the detection of TIL in most tumors directly correlates with improved prognosis and patient survival, and ideally, this interaction completely eliminate the neoplasm. If the immune system does not kill the malignant growth, it may become clinically significant. Conversely, successful antitumor responses may cross-react with normal self-tissues, leading to the loss of self-tolerance. Consequently, if the magnitude of the immune response continues to grow, inflammatory or autoimmune disease may develop [9].

Our case report reviewed and investigated the immunological pathogenesis of DM and drug eruption, suggesting associated pathways between these entities.

In conclusion, we have shown that underlying malignancy may represent a favorable soil for rare immunological reactions such as paraneoplastic DM or a cutaneous drug eruption to paclitaxel. In addition, our case underscores the importance of being vigilant for varied forms of associated immunological reactions in patients with internal malignancy. However, the exact pathophysiological mechanisms behind DM and drug eruption, as seen in our patient, have been the subject of controversy. Although DM and drug eruption are allergic and immune-processes, their specific mechanisms require clarification in further studies.

**CONFLICT OF INTEREST**

The authors declare that they have no competing interests.

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