Occurrence of Dermatomyositis Immediately after Mastectomy Subsequent to Severe Chemotherapeutic Drug Eruption

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Abstract:
We herein report a patient with breast cancer who developed dermatomyositis (DM) immediately after mastectomy. She had a history of severe drug eruption during neoadjuvant chemotherapy six months previously. Within a month after the operation, myalgia and rash, including Gottron's papules, developed, and skeletal-muscle enzymes elevated, so she was diagnosed with probable DM according to the Bohan and Peter criteria. In many neoplastic DM cases, the course of the disease parallels the course of the malignancy. Possible mechanisms were suggested to explain the development of DM in the present case and offer new insight into autoimmune diseases.

Key words: paraneoplastic dermatomyositis, surgery, chemotherapy, severe drug eruption

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Introduction
Dermatomyositis (DM) is a rare idiopathic autoimmune disorder with an annual incidence of approximately 1/100,000, and approximately 10% of patients with DM have an associated malignancy (1, 2). Breast cancer accounts for approximately 20% of malignancies seen in DM patients with malignancy (3). The malignancy usually appeared within 1 year after the diagnosis of DM, and the standardized incidence ratio of malignancy among DM patients was reported to be 17.29 in the first year (4). However, the development of DM after the diagnosis or treatment of malignancy has not been fully evaluated. The molecular mechanisms by which malignancy induces inflammatory myositis is unclear, but several autoantibodies have been detected in DM patients with malignancy (5).

Stevens-Johnson syndrome (SJS) and toxic epidermal necrosis (TEN) are known manifestations of severe drug eruption (6-8), and previous reports have suggested that severe drug eruptions provoke autoimmune disease (9-13).

We herein report a patient with breast cancer who developed a severe drug eruption during neoadjuvant chemotherapy and subsequently developed DM just after mastectomy.

Case Report
A 61-year-old Japanese woman was diagnosed with stage IIIIC invasive ductal breast carcinoma and started neoadjuvant chemotherapy with doxorubicin (DXR) and cyclophosphamide (CYC) (anthracycline/CYC [AC]) in October 2015. During the first course of chemotherapy, she developed erythema on the right shoulder and chest wall, which spread after the second course was started (Fig. 1). Although atypical lymphocytes appeared (2.5%), herpes virus infection was excluded by the Tzanck test, and a dermatologist clinically diagnosed a severe drug eruption similar to SJS caused by AC chemotherapy. Mucous membrane involvement was absent. Prednisolone (PSL) was started at 30 mg/day and then tapered and discontinued 1 month later. She was also treated with weekly paclitaxel instead of AC chemotherapy. Although she developed acute pharyngitis in February, the scheduled 12 courses of chemotherapy was completed, and mastectomy and axillary node dissection were performed in March 2016 (Fig. 2). After the operation, flurbiprofen, pentazocine, loxoprofen, and rebamipide were administered

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temporarily; however, no other drugs such as antibiotics were used.

At the beginning of April, anorexia, malaise, and fatigue developed and worsened daily. Her eyelids became edematous, and she developed slight myalgia; therefore, she visited our hospital. She had a rash on the face, chest, and abdominal wall. No muscle weakness or tenderness was observed, but a laboratory examination revealed a significantly increased creatine kinase (CK) level (1,299 U/L). Drug-induced rash was suspected, and loxoprofen was discontinued, but her cutaneous symptoms worsened; erythema and itching spread to the head, upper back, and extremities, and blisters appeared on the forearm. Furthermore, her proximal myalgia worsened, so she was referred to our department and admitted a week later. She had never been diagnosed with dyslipidemia or taken statins.

On admission, swelling erythemas were found on her eyelids, erythematous papules on the dorsum of the metacarpophalangeal joints, and a flat red rash over the back of the elbows; these rashes are compatible with heliotrope erythema, Gottron’s papules, and Gottron’s sign (Fig. 3). Furthermore, periungual erythema was found with widespread erythema and facial edema (Fig. 3). The blisters were observed on both forearms, and a shawl sign was also observed (Fig. 3). Manual muscle testing showed deltoid and quadriceps weakness, and magnetic resonance imaging showed the enhancement of the deltoid muscle and rotator cuff (Fig. 4). She did not have dysphasia. Laboratory examinations revealed elevated CK (1,181 U/L), myoglobin (854 ng/mL), lactate dehydrogenase (427 U/L), and aspartate transaminase (70 U/L) levels. There was no thyroid dysfunction, and interstitial lung disease was absent. Electromyography and a muscle bi-

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**Figure 1.** Erythema after anthracycline/cyclophosphamide chemotherapy. Millet-sized blisters developed on the trunk with itching.

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**Figure 2.** Clinical course. Acute pharyngitis developed in February and was treated with antibiotics. Unfortunately, CK had never been evaluated before the development of DM. A/C: Adriamycin/cyclophosphamide, CK: creatine kinase, CRP: C-reactive protein, DM: dermatomyositis, LD: lactate dehydrogenase, PSL: prednisolone, PTX: paclitaxel.
opsies were not performed. The histological findings of the blisters was consistent with DM, but myositis-related autoantibodies were undetectable (Table).

A diagnosis of DM was made according to the Bohan and Peter criteria (14). After the initiation of 1 mg/kg/day of PSL, her symptoms, including erythema and muscular weakness, quickly improved, and the serum CK level also decreased. PSL was tapered, and she was discharged at the end of May 2016 (Fig. 2). Because her breast cancer was classified as stage IIIC, adjuvant radiotherapy was required but was not performed due to the skin symptoms. Neither recurrence nor metastasis was detected on computed tomography at the end of April.

**Discussion**

We encountered a case of DM that developed immediately after breast cancer surgery in a patient with a history of severe drug eruption during neoadjuvant chemotherapy. The development of DM after the diagnosis of malignancy is relatively uncommon (15, 16), and the development of DM after the surgical treatment of breast cancer has only been reported once previously, in a case of primary limited systemic sclerosis [calcinosis, Raynaud phenomenon,
esophageal dysmotility, sclerodactyly, and telangiectasis (CREST) syndrome (17). The clinical course of DM is usually correlated with the course of the underlying malignancy (16, 18, 19). To explain the unexpected onset in our case, three mechanisms of pathogenesis are proposed: operative stress, chemotherapy, and severe drug eruption.

The first possible factor related to the development of DM was operative stress. Our patient had never had muscle symptoms before mastectomy, and the symptoms arose after the surgery. Interestingly, a recent study revealed that 15% of patients with Guillain-Barré syndrome, which is also attributed to an autoimmune reaction, underwent a surgical procedure within eight weeks prior to symptom onset (20). Previous reports showed that innate immunity was activated by damage-associated molecular pattern molecules from the injured tissues, resulting in the expression of inflammatory cytokines (21-23). Another report showed that excessive inflammation suppressed cellular immunity and downregulated Th1 cells (24). As the predominance of Th2 cells in DM patients is well-known (25), operative stress may cause DM through robust inflammation and the subsequent imbalance of Th1/Th2 immunity.

The second possible factor is chemotherapy. Generally, chemotherapy induces immunosuppression and relieves autoimmune disease. However, several case reports have found that chemotherapy induced or exacerbated paraneoplastic DM (26, 27). They concluded a short duration from chemotherapy to DM onset might explain the relationship (26, 27). Although the precise mechanism is unknown, chemotherapy may cause exposure of tumor cell antigens and induce autoimmunity.

The third possible factor is drug eruption. A recent study revealed that autoantibodies against cytoskeletal linker protein were detected in the serum of SJS/TEN patients in the early stage as a consequence of epidermal damage (9). Drug hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms, another type of drug eruption, has also been reported to be associated with multiple autoimmune sequelae, including thyroid disease, type 1 diabetes mellitus, and autoantibody productions, suggesting that autoimmune responses occur after severe drug eruptions (10, 11). In these cases of severe drug eruption, herpes viruses are activated after the eruption (28). Virus infection is generally associated with autoimmune diseases (28) and has also been proposed as a cause of the production of myositis-specific antibodies (29). Interestingly, drug eruption was reported in 22% of Japanese patients with adult-onset Still’s disease, and antibodies against various viruses were found in 47% of those patients (30). Thus, severe drug eruption might induce autoimmunity via viral reactivation. Indeed, atypical lymphocytes were detected in the present case. It is possible that DM had already developed at the onset of the first drug eruption but remained undetected because a histological evaluation was not performed at that time and was masked by PSL treatment and/or chemotherapy.

We herein reported a novel case of DM that developed immediately after excision of breast cancer in a patient with a history of severe eruption caused by chemotherapy. Surgery, chemotherapy, and drug eruptions are not specific for breast cancer; therefore, our hypothesis can be applied to all types of malignancy-related DM. Considering possible mechanisms to explain the development of DM in the present case may offer new insight into autoimmune diseases and help clarify the pathogenesis.

Written informed consent for this case report was obtained from the patient.

Author’s disclosure of potential Conflicts of Interest (COI).
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