Occurrence of Cutaneous Marginal Zone B-Cell Lymphoma Post Breast Cancer Chemotherapy: A Case Report

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Primary cutaneous marginal zone B-cell lymphomas (PCMZLs) are classified as low-grade as they run an indolent course. They are histologically characterized through non-epidermotropic nodular or diffuse infiltrates consisting of small or medium heterogeneous atypical lymphoid cells. In the past few years, chemotherapy has increased the survival rate of breast cancer patients. However, the adverse effects of treatment, such as leukemia, have also been shown to emerge gradually. Additionally, cases of occurrence of non-Hodgkin lymphoma (NHL) post chemotherapy have also been reported. A 48-year-old female patient was presented with a violaceous nodule on her left thigh. Around 15 months ago, she completed breast cancer chemotherapy. Eight months later, a skin lesion appeared. Histological findings revealed dense and nodular lymphocyte infiltration. Immunohistochemical staining was positive for CD20 and BCL2. Clinical and histological examination of the lesions confirmed PCMZL. After systemic evaluation, lymphoma was found to be limited to the skin, and thus, she underwent complete excision of the lesion. At the first month follow-up, there was a recurrent lesion on the right wrist, which was excised successfully. However, recurrences occurred again in the calf and forearm in the following five and two months, respectively. These lesions were also confirmed with PCMZL using biopsy. We assume that this case is related to chemotherapy as it was presented and recurred abruptly post chemotherapy. Additionally, there are several reported cases of NHL post breast cancer chemotherapy. However, this is the first case report of PCMZL associated with chemotherapy.

**Keywords:** Breast neoplasms, Drug therapy, Lymphoma

**INTRODUCTION**

Marginal zone B-cell lymphoma (MZL) accounts for approximately 5% of all non-Hodgkin lymphoma (NHL) cases. MZL occurs most commonly in the gastrointestinal tract, and primary cutaneous marginal zone B-cell lymphoma (PCMZL) is rare, accounting for only 11% of all MZL cases. PCMZL usually appears as multifocal plaques or nodules on the trunk and extremities. It is histologically characterized through non-epidermotropic nodular or diffuse infiltrates that consist of small or medium heterogeneous atypical lymphoid cells.

MZL is known to be associated with autoimmune diseases, such as Hashimoto’s thyroiditis and Sjogren’s syndrome. Additionally, it may be associated with Helicobacter pylori, Borrelia burgdorferi, Campylobacter jejuni, Chlamydia psittaci, and hepatitis C virus infections. However, we did not find cases of PCMZL associated with chemotherapy in the literature review. Herein, we report a rare case of PCMZL that developed after chemotherapy with doxorubicin, cyclophosphamide, and paclitaxel.

**CASE REPORT**

A 48-year-old female patient was presented with a violaceous nodule on her left thigh. The lesion appeared at first around seven months ago. About 20 months ago, she was diagnosed with left breast cancer, and thus, she underwent radical mastectomy. She was then treated with radiation therapy (RT) and chemotherapy with doxorubicin, cyclophosphamide, and paclitaxel for five months. Eight months...
after the completion of chemotherapy, a skin lesion appeared.
Initially, she was diagnosed with dermatitis, and thus, treated with a topical steroid at the previous hospital. However, the skin lesion did not improve. Physical examination revealed a solitary, non-tender, 3-cm-sized, soft violaceous, and purpuric nodule on the thigh (Fig. 1). However, there was no skin lesion on the breast. Therefore, biopsy was performed, following which the histological examination revealed the occurrence of dense and nodular lymphocyte infiltration with marginal zone expansion, showing small, round, and cleaved lymphocytes with occasional large cells (Fig. 2). Immunohistochemical staining revealed that the infiltrating cells were positive for CD20, BCL2, and MUM-1 but negative for BCL6, CD3, CD5, and CD10 (Fig. 3). Some reactive follicles were positive for BCL6. IgG staining showed focal positive, confirming that some plasma cells were class-switched. The Ki-67 proliferation index was 10%. Clinical and histological examination of the lesions confirmed PCMZL. Post systemic evaluation, including bone marrow examination, positron emission tomography–computed tomography (CT), chest and abdominal-pelvic CT, gastro-duodenoscopy, and colonoscopy, MZL was confirmed to be limited to the skin. She therefore underwent complete excision of the lesion.

The patient was presented for the one month follow-up. Although the excision site exhibited signs of complete healing, appearance of a recurrent tumor was noted. The recurrent lesion was similar to the first lesion, but this time, it was on the right wrist (Fig. 4A). The patient was diagnosed with PCMZL through biopsy, and the lesion was excised. Again, about five months later, a recurrent lesion appeared on the right calf (Fig. 4B). The lesion was diagnosed with PCMZL through biopsy and successfully excised. Moreover, two months later, a new lesion appeared on the right forearm (Fig. 4C). This lesion was also confirmed with PCMZL through biopsy. We decided not to perform any further invasive procedures and changed the course of treatment to RT. Currently, the patient visits the hospital every three months after getting treated with a total of 3,600 cGy of RT for a month.

**DISCUSSION**

PCMZL are low-grade B-cell lymphomas that run an indolent course. Clinically, PCMZL frequently presents tumoral lesions and infiltrated nodules and plaques. Compared to cutaneous follicular center B-cell lymphomas, PCMZL has been known to predominantly affect the trunk and extremities, followed by the head and neck. Most patients do not exhibit any severe symptoms, such as pruritus or tenderness. Surgical excision or RT are the first-line treatment for PCMZL. A literature review demonstrated that about 99% of PCMZL patients achieve complete remission post RT or excision.

PCMZLs are characterized histologically through a polymorphous lymphocyte proliferation mainly composed of mar-
ginal zone B-cells. These lymphomas exhibit nodular to diffuse infiltrates with sparing of the epidermis. The infiltrates are composed of small lymphocytes, marginal zone B-cells, lymphoplasmacytoid cells, and plasma cells, along with reactive T cells. The marginal zone B-cells exhibit specific cytological characteristics and immunophenotype, as they positive for CD20, CD79a, and bcl-2, and negative for CD5, CD10, and bcl-6, which is different from cutaneous follicle-center lymphoma or the center of reactive follicles.

In the present case, the patient exhibited multiple lesions that occurred sequentially, which were confirmed as primary lesions. There are several reported cases of PCMZL associated with autoimmune disease or infection; however, in the present case, there was no evidence of autoimmune disease or infection. The patient only had a history of treatment with chemotherapy and RT for breast cancer. About eight months after the completion of chemotherapy, the first lesion appeared on the thigh. Furthermore, eight months later, another lesion recurred on the wrist. After that, recurrences occurred in the calf and forearm in the following five and two months, respectively. Per the literature review, the relapse rate of PCMZL is 44% and the median duration until relapse could be 47 months. However, in the present case, there were a total of three relapses within a time span of eight months.

It is well-known that there is a high risk of secondary malignant tumor development in patients treated with chemo-
therapy and/or RT\textsuperscript{5-7}. Myelodysplastic syndrome and acute myeloblastic leukemia are the most frequently developing secondary malignant tumors. Lymphoma development is often associated with high-dose chemotherapy and bone marrow transplantation\textsuperscript{8}. The alkylating agent cyclophosphamide is a widely used chemotherapeutic drug with proven carcinogenic effects. Additionally, the intercalating topoisomerase II inhibitors, such as doxorubicin, are potentially oncogenic, but these effects may not be clinically manifested because of dose-limiting cardiotoxicity. However, the addition of alkylating agents, even at relatively low doses, may lead to cumulative DNA damage sufficient to induce hematological and lymphoreticular diseases\textsuperscript{9}. Therefore, in the present case, cyclophosphamide and doxorubicin are most likely to be associated with PCMZL. In addition to leukemia, several cases of NHL induced upon chemotherapy and RT have been reported\textsuperscript{10-14}. The duration between chemotherapy and lymphoma development have been shown to vary between nine months to three years. In the present case, lymphoma developed eight months after the completion of chemotherapy, which is consistent with previous studies. Since the lesions are scattered throughout the body rather than localized at the radiation site, chemotherapy is more likely to be the devious cause than RT. All cases of lymphoma after RT exhibited lesions on the radiation site\textsuperscript{14-16}.

We consider this case as a chemotherapy-related PCMZL on the following grounds. First, it started to occur eight months after the completion of chemotherapy. This is consistent with the previously reported cases in which lymphoma occurred post chemotherapy. Additionally, three relapses occurred in a short time span post chemotherapy. Second, several cases of other NHLs post chemotherapy have already been reported. Third, it has been well demonstrated that the development of other secondary tumors, such as leukemia, increases post chemotherapy, especially cyclophosphamide. Additionally, the risk of tumorigenesis has been shown to be higher when cyclophosphamide is used in combination with doxorubicin\textsuperscript{9,17}, both of which were administered in the present case. Moreover, PCMZL caused by other drugs such as antihistamines and fluoxetine have also been reported\textsuperscript{18,19}. For these reasons, the possibility of occurrence of PCMZL should be considered when evaluating patients with an incidence of secondary tumor post chemotherapy. Here, we report a rare case of occurrence of PCMZL that recurred repeatedly post breast cancer chemotherapy.

**CONFLICTS OF INTEREST**

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