Case Report

A Rare Case of Blastic Plasmacytoid Dendritic Cell Neoplasm Occurred in Postchemotherapy of Breast Cancer

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Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare and highly aggressive hematologic malignancy that arises from plasmacytoid dendritic cells. BPDCN typically presents with skin lesions and may involve peripheral blood, bone marrow, lymph nodes, or extranodal sites. It usually arises de novo; though some BPDCN cases (10–20%) are associated with or develop into other myeloid neoplasms, most commonly chronic myelomonocytic leukemia (CMML), myelodysplastic syndrome (MDS), or acute myeloid leukemia (AML) [1]. Association with myeloid neoplasms suggests related pathogenesis [1].

The development of various therapy-related myeloid neoplasms (t-MN) following breast cancer chemotherapy has been confirmed [10–12]. However, we have not come across any reports specifically describing BPDCN after chemotherapy of breast cancer. Here, we report a case of 57-year-old female presenting with cervical lymphadenopathy and skin rashes during the COVID-19 pandemic in 2021 following multiple types of postmastectomy therapy for breast cancer. The patient was ultimately diagnosed with BPDCN by lymph node biopsy. To the best of our knowledge, this is the first case report of BPDCN occurring postchemotherapy of breast cancer.

1. Introduction

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare and highly aggressive hematologic malignant neoplasm derived from the precursors of plasmacytoid dendritic cells. BPDCN predominantly occurs in the elderly, although it can occur at any age, including in children [1–3]. Prevalence is approximately 3.3 times higher in males compared to females [1]. BPDCN involves multiple sites and organs, with the highest preference for skin (in 64–100% cases), followed by bone marrow and peripheral blood (80–90% cases), lymph node (40–50% cases), and spleen (20% cases) [4]. Less frequently, it was also shown to affect breast, brain and central nervous system, liver, lung, paranasal sinus, testis, and other sites [1, 5–9].

The etiology of BPDCN remains unknown [1]. There is no known association with EBV [1, 3]. It usually arises de novo; though some BPDCN cases (10–20%) are associated with, or develop into other myeloid neoplasms, most commonly chronic myelomonocytic leukemia (CMML), myelodysplastic syndrome (MDS), or acute myeloid leukemia (AML) [1]. Association with myeloid neoplasms suggests related pathogenesis [1].

The development of various therapy-related myeloid neoplasms (t-MN) following breast cancer chemotherapy has been confirmed [10–12]. However, we have not come across any reports specifically describing BPDCN after chemotherapy of breast cancer. Here, we report a case of 57-year-old female presenting with lymphadenopathy on the left and right sides of her neck, skin rashes, pancytopenia, and blasts in the peripheral blood. The patient was diagnosed with BPDCN six years following mastectomy and chemotherapy for breast cancer. We believe this is the first case report of BPDCN occurring postchemotherapy of breast cancer.

2. Case Presentation

The patient is a 57-year-old Asian female who was diagnosed with cancer of the right breast in July 2015. She first
presented with a palpable 2.0 cm nodule on her right breast. Mammogram taken in July 2015 showed a nodule suspicious for malignancy. Ultrasound showed suspicious regular palpable 1.7 cm mass with adjacent 0.9 cm irregular nodule in the 2:30–3:00 right breast. The patient underwent a surgical core biopsy in July 2015, which showed invasive ductal carcinoma, moderately differentiated (tubule formation score 3/3, nuclear grade score 2/3, and mitoses score 2/3). The invasive ductal carcinoma was strongly positive for estrogen receptor (ER) (>95%) and progesterone receptor (PR) (>95%). HER-2 by immuno-histochemistry was equivocal (score 2+) and negative by fluorescence in situ hybridization (FISH). The Ki-67 proliferation index was 5–10%. The patient underwent right fluoroscopy menstrual bleeding score 3/3). The invasive ductal carcinoma was moderately-highly atypical and the findings can be related to malignancy such as lymphoma. The patient was subsequently hospitalized to our hospital and underwent further work up including lymph node biopsy.

3. Laboratory Studies and CT Studies

Laboratory analysis revealed mild leukopenia (WBC 3.36 K/L), anemia (HB 7.8 g/L), and thrombocytopenia (95 K/UL) with an abnormal differential showing atypical lymphocytes/ blasts 21%, neutrophils 35%, bands 10%, lymphocytes 21%, monocytes 9%, and metamyelocytes 4%. The peripheral blood smear showed the atypical lymphoid cells to be medium-sized, and with scanty cytoplasm, fine chromatin, and small nuclei, resembling lymphoid blasts (Figures 2(a) and 2(b)). COVID-19 testing (SARS-CoV-2 NAAT by real-time PCR of nucleic acid amplification) and CMV testing were not detected. Cytogenetics showed a normal female karyotype observed in 20 analyzed metaphase cells. No numerical or structural abnormalities of clinical significance were found in these cells. FLT3 mutation by PCR is negative for both internal tandem duplication (ITD) and tyrosine kinase domain (TKD). Epstein–Barr Virus (EBV) serology signified a past infection. HIV testing was negative. CT scan showed bilateral diffuse cervical lymphadenopathy along with bilateral intraparotid glands, mediastina, and left axillary lymphadenopathy.

4. Diagnosis

An excisional lymph node biopsy on the right neck was performed. The lymph node architecture was completely effaced by a diffuse proliferation of medium-sized atypical hematopoietic cells with a scant amount of cytoplasm, a round, oval, coffee-bean shaped, or irregular nuclei with indistinct nucleoli (Figures 3(a) and 3(b)). Mitotic figures were frequently identified. By immunohistochemistry, the atypical hematopoietic cells showed immunoreactivity for BCL-2, CD4 (Figure 3(c)), CD33, CD43 (Figure 3(d)), CD45, CD56 (partial and weak) (Figure 3(e)), CD68 (perinuclear dot), CD123 (weak) (Figure 3(f)), and TdT (Figure 3(g)), while they were negative for BCL-1, BCL-6, CD3, CD5, CD8, CD10, CD15, CD20, CD23, CD30, CD34, CD138, CD163, MUM-1, MPO (Figure 3(h)), and PAX-5. CD99 and CD117 are equivocal. P53 shows a wild type staining pattern. The Ki-67 proliferation index was approximately 50–60% (Figure 3(i)). EBER by in situ hybridization was negative. The morphology and immunostaining profile were diagnostic of blastic plasmacytoid dendritic cell neoplasm (BPDCN), and flow cytometry performed on the peripheral blood later confirmed the diagnosis of BPDCN. The patient was transferred to an advanced leukemia and lymphoma center for a clinical trial with Tagraxofusp. Later, the patient received a stem cell transplantation, and she is currently in remission.

5. Discussion

BPDCN is a rare aggressive hematopoietic neoplasm derived from plasmacytoid dendritic precursor cells (type 1 interferon-producing cells or plasmacytoid monocytes). Since this neoplasm was first described by Adachi M’s group in 1994 [13], BPDCN has been referred to by various names, including agranular CD4+ natural killer (NK) leukemia [14],
CD4+/CD56+ hematodermic neoplasm [2, 15], and blastic NK lymphoma [16]. In 2008, the WHO placed this rare neoplasm in the category of AML and related precursor neoplasms [17] following the realization that BPDCN results from the clonal proliferation of immature plasmacytoid dendritic cells (PDC) [18]. In 2016, the WHO classified BPDCN as a distinct neoplastic entity [1]. In normal situations, the PDCs are an essential part of the innate adaptive immune response [19, 20]. These cells respond to bacterial and viral infections and other pathogens by producing alpha-interferon; hence, they are also known as alpha-interferon producing cells or plasmacytoid monocytes. Proliferation of the normal PDCs can occur in autoimmune disorders as well [19, 20].

5.1. Histologic and Immunophenotypic Features. Microscopically, BPDCN is characterized by a diffusely monomorphous proliferation of small to medium-sized hematopoietic cells resembling either lymphocytes or myeloid blasts. Immunohistochemically, the tumor cells usually express CD4, CD43, CD45RA, and CD56, as well as the PDC-associated antigens CD123, CD303, and TCL1A, while they are negative for CD3, CD13, CD16, CD19, CD20,
CD34, lysozyme, myeloperoxidase (MPO), and PAX-5. In addition, they are variably positive for BCL-2, BCL-6, CD33, CD68, CD117, S100, TCF4, and TdT. The proliferation index as assessed by Ki-67 is variable from 20% to 80%. The absence of lineage-associated antigens, together with positivity for CD4, CD45RA, CD56, and CD123 is considered as a unique immunophenotype virtually pathognomonic of BPDCN [21]. CD303 positivity has the highest diagnostic score within a panel of markers used for BPDCN identification [22]. Genetically, T-cell and B-cell receptor gene mutations are usually germline. Specific chromosomal aberrations are absent, but complex karyotypes are commonly present [1].

5.2. Diagnosis and Differential Diagnosis. The diagnosis of BPDCN is based on the clinical manifestation, histology/morphology, immunohistochemistry, and flow cytometry. Because it shows some similar morphological and immunohistochemical features to other malignant neoplasms, extensive immunohistochemistry, flow cytometry, and/or genetic analysis are essential for a definite diagnosis of BPDCN. The differential diagnosis predominantly includes hematopoietic neoplasms and nonhematopoietic neoplasms. The former consists mainly of AML with monocytic differentiation, T-lymphoblastic leukemia/lymphoma, extranodal NK-T-cell lymphoma, mature T-cell lymphoma, myeloid sarcoma, histiocytic sarcoma, and others. The latter includes malignant melanoma, poorly-differentiated carcinoma, and high grade/undifferentiated sarcoma.

5.3. Therapy-Related Myeloid Neoplasms and Post-chemotherapy of Solid Tumors. Therapy-related myeloid neoplasms (t-MN) are thought to be the consequence of mutational events induced by cytotoxic therapy. Cytotoxic agents implicated in therapy-related myeloid neoplasm include alkylating agents, ionizing radiation therapy, topoisomerase II inhibitors, and others [1]. The alkylating agents demonstrated and implicated in t-MN include melphalan, cyclophosphamide, nitrogen mustard, chlorambucil, busulfan, carboplatin, cisplatin, decarbazine, procarbazine, carmustine, mitomycin C, thiopeta, lomustine, ifosfamide, and temozolomide [1, 11, 23]. They have been known for many years to induce t-MN. Studies have demonstrated chromosomal deletions involving the 5q and 7q regions, as well as complex karyotypes and mutation or loss p53 commonly present in these patients [24–27]. These chromosomal losses lead to several gene defects that are involved in haematopoiesis and may trigger the progression to t-MN [28, 29].
5.4. Is BPDCN COVID-19 Vaccine-Related?

COVID-19 vaccines are commonly administered intramuscularly to the arm/deltoid muscle. An association between vaccine administration and the development of ipsilateral axillary and supraclavicular lymphadenopathy has been reported [34, 35]. The incidence of lymphadenopathy varies. One review showed pooled incidence of clinically detected lymphadenopathy after COVID-19 vaccination was 0.4% [35]. A recently published retrospective case series analyzed the mammograms of patients with a history of administration of at least 1 dose of a COVID-19 vaccine within the previous 90 days and identified 23 cases of axillary adenopathy (3%), which is higher than reported rates of axillary lymphadenopathy in otherwise normal mammography (0.02–0.04%) [34, 36]. The incidence of lymphadenopathy was found to be higher in the first 2 weeks following the vaccination, and it usually resolves within 3–6 weeks [34–36]. If lymphadenopathy persists for more than 6 weeks, or becomes worse, an appropriate management strategy should be taken. In our case, the patient developed multiple enlarged lymph nodes throughout the neck bilaterally, within both parotid glands, and mediastinum 1-2 weeks after the second dose of COVID-19 vaccine. The possibility that receiving a second dose of the COVID-19 vaccine initiated or aggravated the lymphadenopathy cannot be disproved. However, we do not have solid evidence to suggest that the vaccine directly caused or resulted in lymphadenopathy. Presently, no published literature provides direct evidence to support that COVID-19 can induce hematological malignant neoplasms.

5.5. Is BPDCN Therapy-Related or Does It Arise De Novo?

In our case, several interesting phenomena were observed. First, the patient had a history of invasive and metastatic breast cancer, and she received chemotherapy including alkylating agent (cyclophosphamide), topoisomerase II inhibitor (doxorubicin/adriamycin), antitubulin agent (paclitaxel), estrogen receptor antagonist (tamoxifen), and aromatase inhibitors (anastrozole). Second, the patient developed BPDCN six years of postchemotherapy, which falls in the range of about 5–10 years after exposure to alkylating agents [1]. Third, the involvement is not local or limited to lymph nodes, but is systemic and extensive, including bone marrow, peripheral blood, and multiple lymph nodes (bilateral diffuse cervical lymphadenopathy along with bilateral intraparotid glands, mediastina, and left axillary lymphadenopathy). Fourth, the patient had no history of myelodysplastic syndrome or related hematopoietic neoplasms before, except breast carcinoma. Fifth, cytogenetics showed a normal female karyotype without any numerical and structural abnormalities. On the one hand, several related factors observed in our patient’s data (presented above) can suggest causality and raise the possibility that BPDCN here may be a therapy-related occurrence. On the other hand, no direct evidence to support such claim exists. Due to the complexity of possible interactive effects of treatment agents, broad timeline, potential interference of additional unknown factors and random process, and the sheer rarity BPDCN in general, the genuine causes cannot be accurately determined.

In conclusion, we reported what we believe is the only case to date of BPDCN occurring postmastectomy and postchemotherapy of breast cancer. The absence of similar case reports and complexity of etiology preclude us from making any conclusions regarding potential causality or relationship between breast cancer chemotherapy and BPDCN. However, given that numerous reports identify a link between chemotherapy agents and other types of t-MNs, we cannot entirely dismiss this possibility. While de novo manifestation remains entirely plausible, we would like to encourage medical practitioners to at least consider BPDCN as a potential risk factor of breast cancer chemotherapy, albeit highly rare and unlikely.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.
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