Severe cytopenia during adjuvant chemotherapy for early breast cancer in a patient with idiopathic CD4+ lymphocytopenia

KAITO MIMURA[1], AKIHIKO SHIMOMURA[1,2], KOJI WATANABE[3], HANAKO KODA[4], KANAKO NAKAYAMA[5], DAI KITAGAWA[5] and CHIKAKO SHIMIZU[1]

[1]Department of Breast and Medical Oncology, National Center for Global Health and Medicine, Tokyo 162-8655; [2]National Center for Global Health and Medicine Research Course in Advanced Medical Specialties, Juntendo University Cooperative Graduate School, Tokyo 113-8421; [3]AIDS Clinical Center; Departments of [4]Surgery and [5]Breast Surgical Oncology, National Center for Global Health and Medicine, Tokyo 162-8655, Japan

Received December 8, 2022; Accepted June 22, 2023

DOI: 10.3892/ol.2023.13943

Abstract. Idiopathic CD4+ lymphocytopenia (ICL) is a rare immunodeficiency disorder characterized by decreased CD4+ T-cell counts in the absence of human immunodeficiency virus (HIV) infection. Similar to HIV infection, ICL is commonly associated with acquired immunodeficiency syndrome-defining cancers, such as Kaposi sarcoma, non-Hodgkin lymphoma and cervical cancer; however, the presentation of breast cancer in a patient with ICL is rare. The current study presented the clinical course of a patient with early breast cancer and ICL. Following surgery, the patient underwent adjuvant chemotherapy comprising doxorubicin plus cyclophosphamide, followed by paclitaxel. The patient's immunodeficiency status required the prophylactic administration of clarithromycin, trimethoprim-sulfamethoxazole and valganciclovir. Throughout the course of chemotherapy, the patient experienced severe complications of febrile neutropenia, anemia, neutropenia and thrombocytopenia, and was eventually forced to discontinue anticancer chemotherapy, as the relative dose intensity (RDI) could not be maintained. Similar hematological complications and reduced RDI, leading to worse outcomes, are also common in patients with HIV infection receiving chemotherapy, suggesting that CD4+ T cell-deficient patients are prone to developing cytopenia during chemotherapy. The present study demonstrates the importance of further data accumulation in patients with ICL with cancer and the development of a methodology for maintaining the RDI.

Correspondence to: Dr Akihiko Shimomura, Department of Breast and Medical Oncology, National Center for Global Health and Medicine, 1 Chome-21-1 Toyama, Shinjuku, Tokyo 162-8655, Japan
E-mail: akshimomura@hosp.ncgm.go.jp

Abbreviations: ICL, idiopathic CD4+ lymphocytopenia; HIV, human immunodeficiency virus; RDI, relative dose intensity; CMV, cytomegalovirus; ER, estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor 2; TMP-SMZ, trimethoprim-sulfamethoxazole; VGCV, valganciclovir; AC, doxorubicin plus cyclophosphamide; PTX, paclitaxel

Key words: febrile neutropenia, anemia, neutropenia, thrombopenia, immunodeficiency, opportunistic infection, human immunodeficiency virus, acquired immunodeficiency syndrome, relative dose intensity

Introduction

Idiopathic CD4+ lymphocytopenia (ICL) is a rare immunodeficiency disorder characterized by a decrease in CD4+ T cells, an increased risk of opportunistic infections and no evidence of infection with human immunodeficiency virus (HIV) types 1 and 2 or any other known immunodeficiencies or therapies that may decrease T-cell numbers (1). In addition to various opportunistic bacterial, viral, parasitic and fungal infections, patients with ICL frequently experience autoimmune diseases, including Sjögren's syndrome, systemic lupus erythematosus and rheumatoid arthritis (1).

Similar to patients with HIV, patients with ICL frequently experience acquired immunodeficiency syndrome-defining cancers, such as Kaposi sarcoma, non-Hodgkin lymphoma and cervical cancer (1). Due to the rarity of cases, it remains unclear whether the incidence of other cancer types in patients with ICL differs from those without ICL, and various studies have described the incidence of malignancies that coincide with ICL (1-4). According to a meta-analysis of HIV-infected patients, HIV infection does not increase the incidence of breast cancer (5), which may be applied to ICL.

The present study reported on a rare case of early breast cancer in a patient with ICL who experienced a severe complication of neutropenia during adjuvant chemotherapy and was forced to discontinue anticancer therapy.

Case report

In January 1994, a 41-year-old female patient had been diagnosed with cytomegalovirus (CMV) retinitis. In August 2001, on initial presentation to the Center Hospital of the National Center of Global Health and Medicine (Tokyo,

Japan) at the age of 49 years due to the progression of CMV retinitis, a CD4+ T-cell count of 112 and 102/mm^3 (normal range, 500-1,500/mm^3) was determined in two consecutive peripheral blood counts. The patient had no abnormalities in B-cell count, ranging around 150/mm^3 (normal range, 100-600/mm^3) in several tests, with normal IgM and IgG production, and diminished IgA production of 68 mg/dl (normal range, 110-410 mg/dl). The patient's natural killer cell activity exhibited a deficiency, which was 5% (normal range, 18-40%). Bone marrow aspiration and biopsy indicated no abnormalities. The patient displayed no numerical or morphological abnormalities in red blood cells, neutrophils, monocytes or platelets. The patient tested negative for HIV antibodies, without any known other factors that may decrease the CD4+ T cells, which led to the diagnosis of ICL. Of note, the patient had no remarkable family history.

In June 2003, at the age of 50 years, the patient was diagnosed with *Mycobacterium avium* complex lung disease and was administered 400 mg/day of clarithromycin. In May 2017, at the age of 65 years, the patient was diagnosed with type 1 diabetes due to the occurrence of diabetic ketoacidosis, and contrast-enhanced computed tomography during hospitalization adventitiously revealed a contrast effect of the right breast (Fig. 1). Ultrasonography was performed, with no suspected malignancy, and the patient was instructed to undergo a biyearly follow-up. After two years, in September 2019, follow-up ultrasonography (Fig. 2A and B) and mammography revealed a 22x22x8 mm mass with calcification in the right breast and a core needle biopsy was performed. Pathological examination revealed invasive ductal carcinoma, estrogen receptor (ER)-, progesterone receptor (PgR)+, human epidermal growth factor 2 (HER2) 3+ and a Ki-67 index of 30-40%. Subsequently, a right breast resection and sentinel lymph node biopsy were performed. Sentinel lymph nodes were negative for breast cancer metastasis and axillary clearance was not performed. The final pathological results demonstrated invasive ductal carcinoma, ER-, PgR-, HER2 1+ and a Ki-67 index of 30-40%.

As the patient had an immunodeficiency, prophylactic administration of clarithromycin (400 mg/day), trimethoprim-sulfamethoxazole (TMP-SMZ) (1 g/day), and valganciclovir (VGCV) (900 mg/day for 1 week followed by a resting period of 2 weeks) were initiated to prevent opportunistic infections during adjuvant chemotherapy. Initially, doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) were administered. On day 14, the patient experienced febrile neutropenia and cefepime (2 g every 12 h) was administered. On day 16, the white blood cell count decreased to 160/mm^3 (normal range, 4,500-11,000/mm^3), with a neutrophil count of 0/mm^3 (normal range, 2,500-7,000/mm^3; grade 4 neutropenia). Consequently, the next three cycles were administered in combination with pegfilgrastim and levofloxacin prophylaxis. After four cycles, the peripheral hemoglobin levels dropped to 7.4 g/dl (normal range, 11.6-15.0 g/dl; grade 3 anemia) and a red blood cell transfusion of two units was performed. Subsequently, weekly paclitaxel (80 mg/m^2) was administered. The first cycle of paclitaxel was delayed because the peripheral blood count revealed a platelet count of 27,000/μl (normal range, 150,000-450,000/μl; grade 3 thrombocytopenia) and a neutrophil count of 720/mm^3 (grade 3 neutropenia). After a 3-week delay, paclitaxel was administered at the patient's request, despite persistent grade 3 neutropenia. After three cycles of weekly paclitaxel, the treatment was interrupted because a neutrophil count of 740-1,180/mm^3 persisted for 3 weeks, eventually leading to the discontinuation of adjuvant chemotherapy. At this time, bone marrow testing to rule out other underlying hematological malignancies such as myelodysplastic syndrome was considered, although not performed, and replaced by careful follow-up of the peripheral blood count, blood smear and reticulocyte counts. Subsequently, the patient's hematopoiesis recovered to baseline, diminishing the possibility of other hematological malignancies or bone

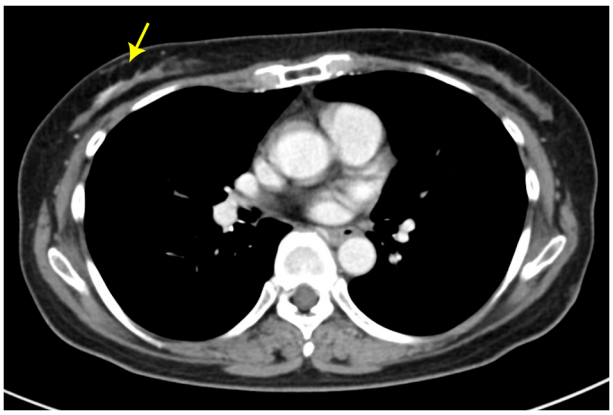

Figure 1. Computed tomography revealed a contrast effect in the right breast (indicated by arrow).

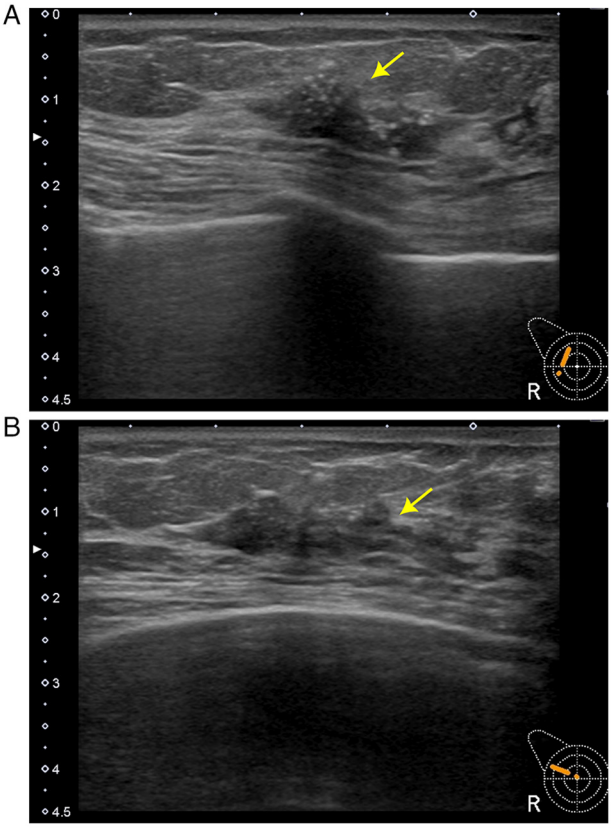

Figure 2. (A) Anti-radial and (B) radial views from ultrasonography of the right breast. The arrows indicate an irregular hypoechoic region accompanied by fine echogenic spots.

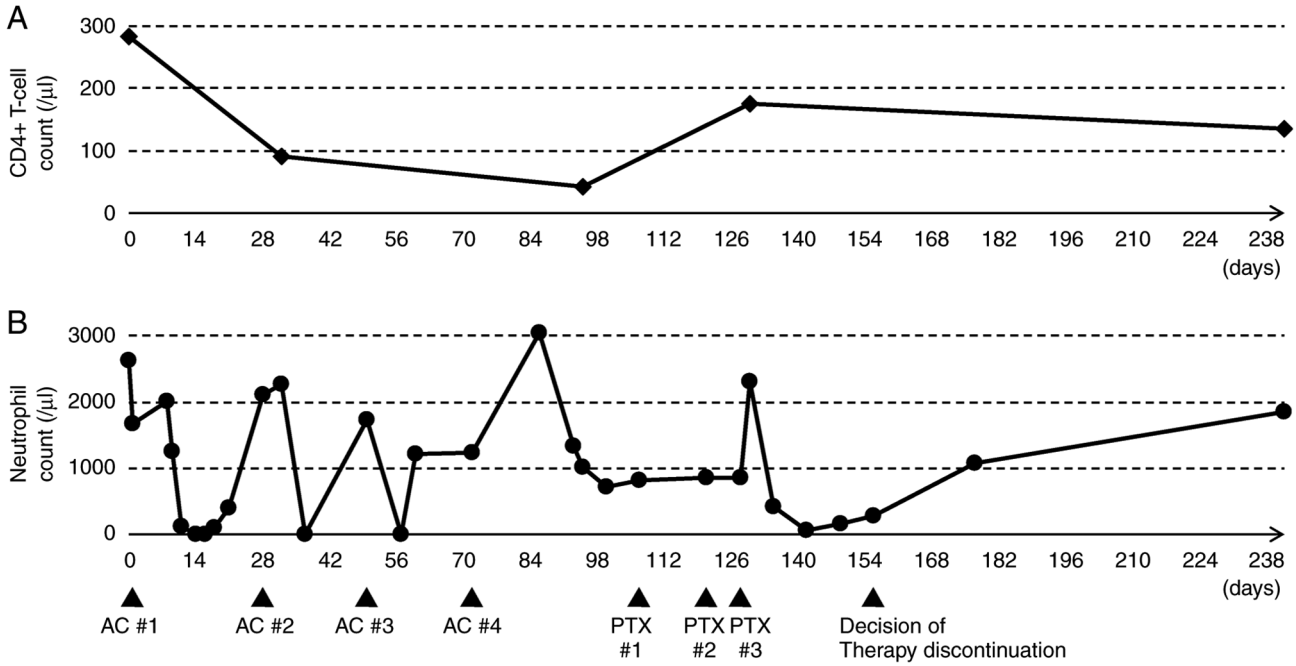

Figure 3. Timeline graph depicting the relation between chemotherapy cycles and blood counts. The relationship between chemotherapy cycles with (A) CD4+ T-cell counts and (B) neutrophil counts is provided. AC, doxorubicin plus cyclophosphamide; PTX, paclitaxel.

marrow failure. No evidence of relapse was observed during the next 2-year and 2-month follow-up. No new complications occurred since the discontinuation of therapy. Fig. 3A and B represent a timeline graph showing the chemotherapy cycles and blood counts during the course of treatment in the present case.

Discussion

The present case report describes a patient with a rare combination of ICL and breast cancer. To the best of our knowledge, this is the first report describing the detailed clinical course of this combination. The patient experienced severe cytopenia throughout the course of adjuvant chemotherapy and was forced to discontinue treatment.

Although the genetic etiologies are unclear in most patients with ICL, certain studies have reported various germline deficiencies in genes associated with T-cell development, hematopoiesis and cytokine signaling (1,3,4). Clinical features of this patient may suggest monoMAC syndrome, a disorder sharing multiple presentations with ICL (6), but appeared unlikely due to the absence of a family history, disorders in B cells and monocytes, and absent hallmarks of underlying bone marrow failure. Furthermore, normal presentations in bone marrow testing and no abnormalities in follow-up blood smears lowered the possibility of myelodysplastic syndrome. Detailed profiling of T cells and genetic testing have not been performed in this patient due to the lack of patient request, which may provide a clue to the pathogenesis of ICL and cytopenia during chemotherapy. As the relationship between the incidence of cytopenia during anticancer chemotherapy and ICL remains unclear, further data accumulation is crucial.

Research on chemotherapy administration for HIV-infected patients in the pre-antiretroviral therapy era demonstrates a highly elevated risk of opportunistic infections in patients with CD4+ T-cell deficiency, such as those treated with liposomal doxorubicin (7), paclitaxel (8), and a combination of cyclophosphamide, doxorubicin and etoposide (9). Therefore, prophylactic drug administration against opportunistic infections is crucial in the management of CD4+ T cell-deficient patients (10). Among the prophylactic drugs used, TMP-SMZ and VGCV commonly cause cytopenia (11). TMP-SMZ decreases blood counts by inhibiting folate metabolism, consequently downregulating granulopoiesis and erythropoiesis. Folate supplementation may have reversed this side effect (11), and pentamidine, dapsone and atovaquone may replace TMP-SMZ (10), although this was not attempted in the present case. VGCV is myelotoxic and a higher dose (900 mg/day) is significantly associated with leucopenia (12). In transplant patients, a meta-analysis revealed that a lower dose of VGCV (450 mg/day) had equivalent effects on the prevention of CMV infection and a lower risk of leukopenia than a higher dose (900 mg/day) (13), which may be considered in patients with ICL. The present case had a history of CMV retinitis and required secondary prophylaxis; therefore, a lower dose was not administered.

Cytopenia during chemotherapy may be attributed to CD4+ T-cell deficiency. Studies on patients with breast cancer and HIV, a condition that also decreases the number of CD4+ T cells, have reported elevated chemotherapy-related hematological toxicity (14). Another study demonstrated a lower relative dose intensity (RDI) in patients with breast cancer with HIV infection, leading to worse outcomes (15). Multiple studies have reported life-threatening cytopenia in HIV-infected patients receiving anticancer chemotherapies (16-18). The effects of antiretroviral therapies, commonly causing drug-drug interactions, cannot be disregarded; however, similar complications in patients with HIV

and ICL receiving chemotherapy give rise to the possibility that CD4+ T cell-deficient patients are prone to develop cytopenia during chemotherapy.

The present study reported a rare case of breast cancer occurring in a patient with ICL. The patient experienced unusually severe cytopenia that led to treatment discontinuation. The present study describes only a single case, which limits the evidence regarding patients with ICL being more prone to developing severe cytopenia and requiring particular attention to complications such as opportunistic infections compared to those without. In the future, cohort studies of patients with ICL undergoing anticancer chemotherapy should be performed to support this conclusion. Further investigations into the relationship between ICL and cancer, the causes of cytopenia and the methodology for maintaining the RDI in CD4+ T cell-deficient patients may benefit patients with both ICL and HIV.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions

KM drafted the manuscript. AS revised the manuscript. KM, AS, KW, HK, KN, DK and CS were involved in the treatment of the patient. All authors read and approved the final manuscript. KM and AS confirm the authenticity of the raw data.

Ethics approval and consent to participate

This study was exempt from ethical approval by the National Center for Global Health and Medicine Institutional Review Board (Tokyo, Japan). Written informed consent for participation was obtained from the patient.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of this case report and accompanying images.

Competing interests

The authors have no competing interests to declare.

References

1. Walker UA and Warnatz K: Idiopathic CD4 lymphocytopenia. Curr Opin Rheumatol 18: 389-395, 2006.
2. Ahmad DS, Esmadi M and Steinmann WC: Idiopathic CD4 lymphocytopenia: Spectrum of opportunistic infections, malignancies, and autoimmune diseases. Avicenna J Med 3: 37-47, 2013.
3. Régent A, Autran B, Carcelain G, Cheynier R, Terrier B, Muylder BCD, Krivitzky A, Oksenhendler E, Costedoat-Chalumeau N, Hubert P, *et al*: Idiopathic CD4 lymphocytopenia: Clinical and immunologic characteristics and follow-up of 40 patients. Medicine (Baltimore) 93: 61-72, 2014.
4. Yarmohammadi H and Cunningham-Rundles C: Idiopathic CD4 lymphocytopenia: Pathogenesis, etiologies, clinical presentations and treatment strategies. Ann Allergy Asthma Immunol 119: 374-378, 2017.
5. Shiels MS, Cole SR, Kirk GD and Poole C: A meta-analysis of the incidence of non-AIDS cancers in HIV-infected individuals. J Acquir Immune Defic Syndr 52: 611-622, 2009.
6. Chu VH, Curry JL, Elghetany MT and Curry CV: MonoMAC versus idiopathic CD4+ lymphocytopenia. Comment to Haematologica. 2011;96(8):1221-5. Haematologica 97: e9-e11, 2012.
7. Hengge UR, Esser S, Rudel HP and Goos M: Long-term chemotherapy of HIV-associated Kaposi's sarcoma with liposomal doxorubicin. Eur J Cancer 37: 878-883, 2001.
8. Saville MW, Lietzau J, Pluda JM, Feuerstein I, Odom J, Wilson WH, Humphrey R, Feigel E, Steinberg S and Broder S: Treatment of HIV-associated Kaposi's sarcoma with paclitaxel. Lancet 346: 26-28, 1995.
9. Sparano JA, Hu X, Wiernik PH, Sarta C, Reddy DM, Hanau L and Henry DH: Opportunistic Infection and immunologic function in patients with human immunodeficiency virus-associated Non-Hodgkin's lymphoma treated with chemotherapy. J Natl Cancer Inst 89: 301-307, 1997.
10. Torres HA and Mulanovich V: Management of HIV infection in patients with cancer receiving chemotherapy. Clin Infect Dis 59: 106-114, 2014.
11. Khalil MAM, Khalil MAU, Khan TFT and Tan J: Drug-induced hematological cytopenia in kidney transplantation and the challenges it poses for kidney transplant physicians. J Transplant 2018: 9429265, 2018.
12. Brum S, Nolasco F, Sousa J, Ferreira A, Possante M, Pinto J, Barroso E and Santos J: Leukopenia in kidney transplant patients with the association of valganciclovir and mycophenolate mofetil. Transplant Proc 40: 752-754, 2008.
13. Kalil AC, Mindru C and Florescu DF: Effectiveness of valganciclovir 900 mg versus 450 mg for cytomegalovirus prophylaxis in transplantation: Direct and indirect treatment comparison meta-analysis. Clin Infect Dis 52: 313-321, 2011.
14. Singh SN, Zhu Y, Chumsri S, Kesmodel S, Gilliam BL and Riedel DJ: Outcomes and chemotherapy-related toxicity in HIV-infected patients with breast cancer. Clin Breast Cancer 14: e53-e59, 2014.
15. Martei YM, Narasimhamurthy M, Setlhako DI, Ayane G, Ralefala T, Chiyapo S, Gross R, Shulman LN, Grover S and DeMichele A: Relative dose intensity and pathologic response rates in patients with breast cancer and with and without HIV who received neoadjuvant chemotherapy. JCO Glob Oncol 8: e2200016, 2022.
16. Ngidi S, Magula N, Sartorius B, Govender P and Madiba TE: Incidence of chemotherapy-induced neutropenia in HIV-infected and uninfected patients with breast cancer receiving neoadjuvant chemotherapy. S Afr Med J 107: 595-601, 2017.
17. Bundow D and Aboulafia DM: Potential drug interaction with paclitaxel and highly active antiretroviral therapy in two patients with AIDS-associated kaposi sarcoma. Am J Clin Oncol 27: 81-84, 2004.
18. El-Rayes BF, Berenji K, Schuman P and Philip PA: Breast cancer in women with human immunodeficiency virus infection: Implications for diagnosis and therapy. Breast Cancer Res Treat 76: 111-116, 2002.