Breast Cancer: Basic and Clinical Research

CASE REPORT

Adjuvant Chemotherapy for Breast Cancer in a Patient with Primary Autoimmune Neutropenia

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Abstract: We report an extremely rare and complex case of a 44-year-old woman diagnosed with an early stage triple negative breast cancer in the setting of primary autoimmune neutropenia with a pre-existing severe neutropenia. This case-report demonstrates that adjuvant chemotherapy for breast cancer can be administered in a patient with severe neutropenia. The management is however complicated and requires careful monitoring of side-effects related to both chemotherapy and treatment of autoimmune neutropenia. The role of chemotherapy in the treatment of triple negative breast cancer, the approach to autoimmune neutropenia and potential interactions are reviewed. To our knowledge, this is the first case reporting on the use of chemotherapy in a patient with severe pre-existing primary autoimmune neutropenia.

Keywords: breast cancer, autoimmune neutropenia, chemotherapy

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Background

Breast cancer

Breast cancer is the most common type of cancer diagnosed in women. Breast cancers are represented by a heterogeneous group of tumors, characterized by a wide spectrum of clinical, pathologic, and molecular features.[1,2] Traditional prognostic markers for breast cancer include estrogen receptor (ER), progesterone receptor (PR), and HER2/neu. Negative staining for these three markers defines the "triple-negative" phenotype. Patients classified as triple negative have a poor prognosis[3] and have been shown in neoadjuvant studies to be responsive to chemotherapy.[4] Neither hormonal therapy nor HER2-targeted therapy is indicated in triple-negative disease,[5] thus chemotherapy remains the mainstay of systemic adjuvant therapy. So far, there are no standard therapeutic regimens for triple-negative breast cancer and patients remain with a relatively poor prognosis.

Autoimmune neutropenia

The autoimmune neutropenias (AIN) are classified as primary or secondary. Medical conditions that can present with secondary AIN include systemic autoimmune disorders such as Felty's syndrome, systemic lupus erythematosus (SLE), and rheumatoid arthritis, infectious agents such as ParvoB19 and HIV, hematological malignancies including B-cell lymphomas and T-cell lymphomas such as large granular lymphocytic leukemia/lymphoma, non-hematological malignancies, and drug-related.[6] The primary AINs are, in most cases, thought to be caused by the production of anti-neutrophil antibodies. Primary AIN in adults is often a chronic disease with higher prevalence in females. There is a wide range in clinical manifestations; however, it is usually a self-limited condition[7] and is usually treated with antibiotics for documented infectious episodes. Treatment with granulocyte colony stimulating factors is currently the first line therapy. Cyclosporin A, sirolimus and IVIG have also been found to be helpful in some cases.[8,9] There are case reports on the use of rituximab and campath-1H for severe cases of AIN that have not responded to conventional therapies.[10,11]

In this case report, we demonstrate the feasibility of administering chemotherapy to a patient with AIN. This case is complex in view of the risk of infections inherent to the underlying condition (AIN) and use of myelosuppressive chemotherapy, and the potential interactions between chemotherapy with cyclosporin A. Although autoimmune disorders may improve while on chemotherapy, there are no data in the literature detailing the impact of chemotherapy in patients with underlying AIN.

The Case

The patient was diagnosed with primary autoimmune neutropenia (AIN) at age 33, manifesting as recurrent soft tissue and pulmonary bacterial infections. Her baseline absolute neutrophil count (ANC) ranged from 0.1 to 0.2×10^9/L. Investigations for a secondary cause such as an autoimmune disorder, hematological and non-hematological malignancies remained negative. Pertinent investigations included absence of antinuclear antibodies (ANA), rheumatoid factor, and human immunodeficiency virus 1/2 antibodies and related-antigens. Clonal T-cell and B-cell lymphoid neoplasms were excluded by immunophenotyping of a bone marrow aspirate sample. The absence of monoclonal gene rearrangements involving immunoglobulin heavy chains and T-cell receptor beta and gamma chains by polymerase chain reaction was demonstrated in tissue obtained from the axillary lymph node dissection (at the time of breast cancer diagnosis). Trials of growth factors, intravenous immunoglobulin (IVIG), methotrexate, and steroids proved to be of limited benefits in increasing the ANC. She responded to cyclosporin A at 75 mg per os (p.o.) twice a day (BID) and maintained an ANC of approximately 0.6 to 0.7×10^9/L. Her past medical history is significant for asthma, migraine headaches and benign heart palpitations.

At age 44, she presented with a tender left breast lump. There was no associated skin change or nipple discharge. She had no history of previous breast abnormalities and no known family history of breast or ovarian cancer. She had no specific risk factor for breast cancer. Bilateral mammogram revealed a poorly marginated 2.5 cm spiculated mass in the mid to posterior third of the left breast at the 10 to 11 o'clock position. This was associated with numerous pleomorphic calcifications (Fig. 1). Ultrasound examination confirmed the presence of a solid irregular mass. Fine needle aspiration revealed ductal carcinoma. She was treated with a lumpectomy and axillary node dissection. The pathology revealed a 2.9 cm invasive ductal carcinoma: grade III with no

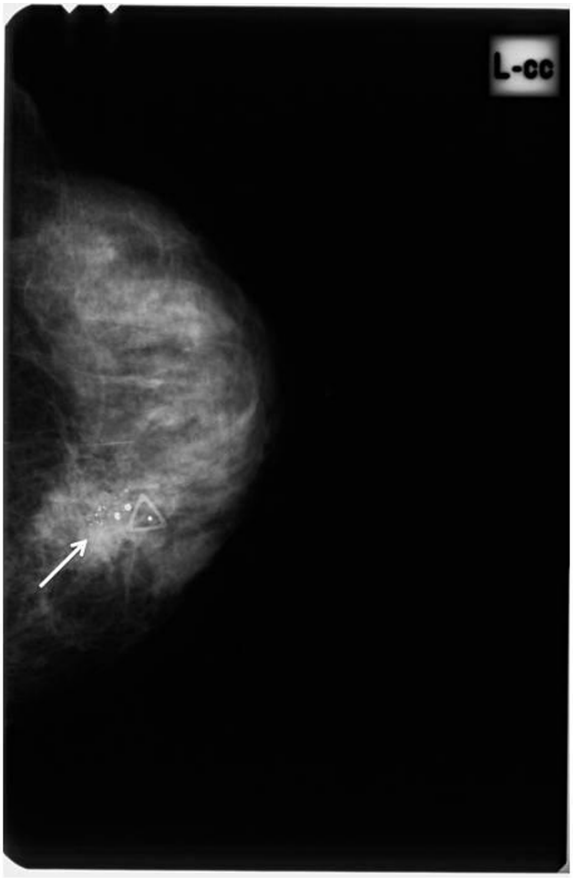

Figure 1. LCC mammogram image shows a ill-defined spiculated mass in the medial quadrant of left breast with associated pleomorphic calcifications (arrow).
Note: Findings are suspicious for malignant breast carcinoma.

lymph node involvement or lymphovascular invasion. The cancer was ER negative (0%), PR negative (0%), and HER-2 negative (0%) by immunohistochemistry (triple negative). Staging investigations including plain chest roentgenogram and bone scan were negative for definite evidence of metastatic disease and she was considered to have stage IIA breast cancer. Her blood work revealed a normal complete blood count (CBC) except for an ANC of 0.9×10^9/L. Creatinine, alanine aminotransaminase (ALT), and alkaline phosphatase (ALK) were normal.

Treatment of breast cancer

Systemic chemotherapy was recommended as adjuvant treatment understanding that her baseline risk of recurrent disease was increased by her relatively young age and the high grade, triple negative pathology. Chemotherapy can be associated with significant improvement in disease free survival and overall survival, especially in women with triple negative breast cancer.[1,2,12] However, the choice of chemotherapy regimen and its safety in a patient with AIN on cyclosporine A, remains to be determined. Prior to the start of chemotherapy, a trial of higher dose of cyclosporin A (150 mg po BID) and granulocyte colony stimulating factor (filgrastim 300 microgram (mcg) sub-cutaneous (s.c.) daily) for 7 days was completed and resulted in significant increase in the white blood cell (WBC) count (12.0×10^9/L) and ANC (7×10^9/L). Upon careful review of the risks and benefits of chemotherapy and potential interactions with cyclosporine A, we elected to proceed with FEC-100 (5-fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, cyclophosphamide 500 mg/m^2) chemotherapy every three weeks for six cycles. Her chemotherapy dose was reduced by 20% at cycle one to reduce the risk of infectious complications. In addition, daily filgrastim (300 mcg s.c.) was added as primary prevention of bacterial infections and cyclosporine A dose was continued at the increased dose of 150 mg po BID. She was admitted 11 days post cycle one for febrile neutropenia with an ANC of 0.1×10^9/L. No focus of infection was identified. She was treated with intravenous antibiotics for two days then discharged home on oral antibiotics. She proceeded to receive cycle two at the previously administered dose reduction. Prophylactic antibiotic treatment with an oral fluoroquinolone was added. Mild renal insufficiency was noted, additional hydration was provided and cyclosporin A dose was reduced to 75 mg po BID. She had an episode of fever and mouth sores 18 days post chemotherapy. Total WBC was 24.7×10^9/L and ANC count was 22.8×10^9/L. No clear focus of infection was identified. She was admitted for a second episode of FN and significant nausea and vomiting after the fifth cycle of chemotherapy. Computerized tomography (CT) of the abdomen was ordered in hospital to investigate nausea and vomiting which eventually subsided. The CT abdomen revealed a left adrenal mass (in keeping with an adenoma), fatty liver, bulky spleen, and several sub centimeter lymph nodes within the retroperitoneum. CT chest completed at the same time revealed small indeterminate pulmonary nodules. The final, sixth cycle of adjuvant chemotherapy was cancelled considering the high risk of complications despite all prophylactic measures. Summary of ANC levels while on chemotherapy are provided in Figure 2. She remained asymptomatic and completed adjuvant radiation therapy to the breast without

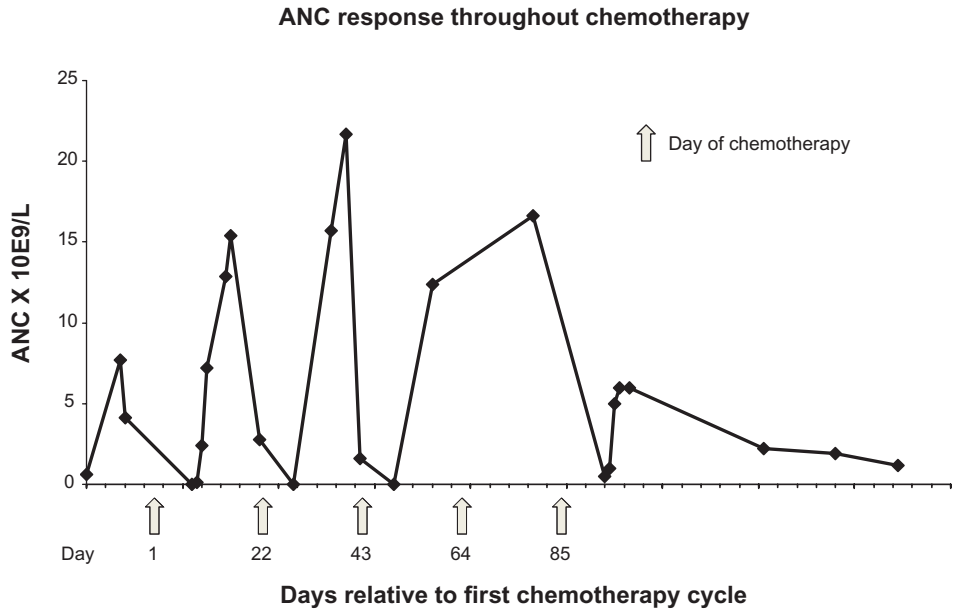

Figure 2. Levels of absolute neutrophil counts (ANC) × 10^9/L before and during chemotherapy.
Note: Days of chemotherapy administration are shown with arrows.

complications. She was followed by respirology after completing chemotherapy. CT scans of the chest were done at regular intervals (~3 months), bronchoscopy and lung biopsies did not reveal evidence of cancer recurrence or infection. Written consent was obtained from a family member.

Recurrence

Eleven months following completion of chemotherapy (at age 45), she presented with rapidly progressive dyspnea. Restaging CT imaging revealed numerous liver lesions, extensive mediastinal and hilar adenopathy, and numerous bilateral lung nodules (Figure 3). Liver biopsy diagnosed metastatic adenocarcinoma consistent with breast cancer recurrence (ER, PR, HER-2 negative). She experienced a rapid pulmonary decompensation and opted for supportive measures. She died within 25 days of identifying the recurrent metastatic disease.

Special Interactions

Cyclosporin A is an immunosuppressant approved for use in patients with psoriasis, rheumatoid arthritis, nephritic syndrome, and following solid organ or bone marrow transplantations. Cyclosporin A binds to the immunophilin cyclophilin A and inhibits the calcium-dependent serine/threonine phosphatase calcineurin, abrogating transcription of interleukin-2 and other lymphokines. Toxicities of cyclosporin A may include decreased renal function (transient and permanent), neurologic tremor, convulsions and infectious complications. Prolonged use of immunosuppressive agents such as cyclosporin A has been found to increase the long-term risk of various malignancies but not breast cancer.[13,14] The use of

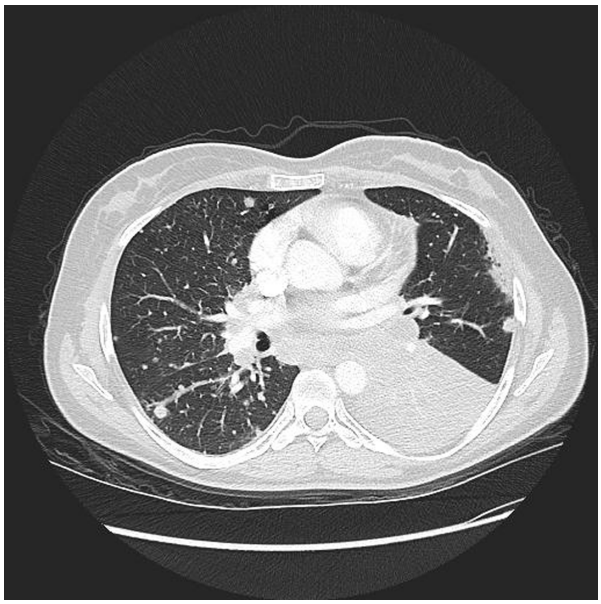

Figure 3. Axial CT image with lung window shows multiple round lesions both lungs in keeping with metastases.
Note: There is collapse of left lower lobe due to obstruction of lower lobe bronchus (not shown) by mass at hilum.

cyclosporine A alone requires ongoing careful vigilance for untoward side-effects related to this agent. The combination of cyclosporin A with chemotherapy agents is complex as cyclosporin A can interact with a number of these agents. In the adjuvant setting for breast cancer, cyclosporine A can compete with the isoenzyme 3A4 and reduce the elimination of cyclophosphamide and taxanes. Cyclosporin A can block the oxidation of methotrexate to its inactive metabolite. This can lead to increased chemotherapy toxicity. Conversely, methotrexate can increase the serum concentration of cyclosporin A and increase the risk of associated toxicities. Careful monitoring for side effects related to both chemotherapy and cyclosporin A is needed when these agents are used in combination.

There is the potential synergistic effect between CSA and chemotherapy. At the cellular level, cyclosporin A is a broad-spectrum multidrug resistance (MDR) modulator and has been shown to increase drug uptake in cells over-expressing P-glycoprotein, MRP-1, breast cancer resistance protein, or lung resistance protein.[15] Its use in combination with chemotherapy could modulate MDR effect and theoretically increase the therapeutic effectiveness of chemotherapy by increasing the amount of active drug intracellularly as a result of biochemical interactions or effects on drug transport across the cell membrane.[16]

Conclusions

Autoimmune neutropenia is an uncommon diagnosis and there is limited information on the feasibility of administering myelosuppressive chemotherapy for solid tumors in this patient population. This case-report demonstrates that multi-agent chemotherapy can be administered in the setting of AIN that presented with a pre-existing severe neutropenia. However, the management of these patients requires careful monitoring of side-effects related to both chemotherapy and CSA. In this case, the early breast cancer relapse and fulminant progression soon after completing adjuvant chemotherapy raise concerns about the impact of chronic immunosuppression on cancer progression.

Author Contributions

MT developed and reviewed the manuscript for content and edits. MT provided data on the molecular analyses. KD provided the radiological data and reviewed the manuscript for content and edits. JP reviewed and summarized patient data, and reviewed the manuscript for content and edits. SB provided the pharmacologic data and reviewed the manuscript for content and edits. PW provided patient data and reviewed the manuscript for content and edits. LB developed and reviewed the manuscript for content and edits, collected patient data, and reviewed the literature.

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Competing Interests

Author(s) disclose no potential conflicts of interest.

Disclosures and Ethics

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