Case Report

Cyclophosphamide and epirubicin-induced diabetes mellitus in breast cancer: A rare occurrence

Pramod Kumar Sharma, Arup Kumar Misra, Vikram Singh[1], Ajay Gupta, Shrishti Saroha, Surjit Singh

Departments of Pharmacology and [1]Medicine, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India

Received: 01-05-2016 **Revised: 27-05-2016** **Accepted: 15-07-2016**

ABSTRACT

Breast cancer is the leading cause of death in women. Epirubicin and cyclophosphamide (EC) is one of the chemotherapeutic regimens used for the treatment of breast cancer. We describe a case treated with EC regimen and who presented to us with symptoms suggestive of diabetes mellitus postchemotherapy. Absence of family history of diabetes and normal blood sugar level, prechemotherapy points toward drug-induced hyperglycemia. These chemotherapeutic agents capable of altering immune response and might act synergistically to cause immunological damage to the islets of pancreas which might precipitate diabetes mellitus. Causality analysis on Naranjo's scale indicates a possible association with regimen.

Key words: Cyclophosphamide, diabetes mellitus, epirubicin, hyperglycemia

INTRODUCTION

Breast cancer is one of the leading cancers and causes of mortality in women.[1] It affects about 12% of women worldwide and 21% in Indian women.[1,2] Chemotherapeutic agents play a major role as adjuvant therapy in the treatment of breast cancer.[3] Chemotherapeutics acts by interfering with DNA synthesis of the metastatic cells and kill them.[4,5] These agents in addition to the cytotoxic effects on the metastatic cells also bring adverse effects in the form of interference with metabolic phenomena in the body. The commonly used chemotherapeutic agents in breast cancer are doxorubicin, cyclophosphamide (CY), paclitaxel, docetaxel, 5-fluorouracil, epirubicin, methotrexate, trastuzumab, pertuzumab, and carboplatin.[6] The chemotherapeutic agents used, epirubicin and cyclophosphamide (EC) may potentially alter immune system by reducing a number of helper T-cells and an increase in the cytotoxic T-cells number. Such alteration in immune response may probably have destructive effects on the beta cells which can be irreversible and thus leads to persistence of hyperglycemia.

Access this article online	
Quick Response Code:	Website: www.jpharmacol.com
	DOI: 10.4103/0976-500X.189684

CASE REPORT

The present case, a 51-year-old postmenopausal female, weighing 56 kg with diagnosis of ductal invasive carcinoma of the right breast presented to us postsurgery and chemotherapy. She was being treated with oral anastrozole 1 mg and oral

Address for correspondence:
Arup Kumar Misra, Department of Pharmacology, All India Institute of Medical Sciences, Jodhpur - 342 005, Rajasthan, India.
E-mail: arup2003m@gmail.com

How to cite this article: Sharma PK, Misra AK, Singh V, Gupta A, Saroha S, Singh S. Cyclophosphamide and epirubicin-induced diabetes mellitus in breast cancer: A rare occurrence. J Pharmacol Pharmacother 2016;7:146-8.

calcium 500 mg once a day for the past 3 months. The diagnosis of the malignancy was confirmed in the month of June 2015 for which she underwent modified radical mastectomy in July 2015. Postsurgery, she received four cycles of chemotherapy (EC regimen) with injection epirubicin 16 mg and injection CY 1 g once daily for consecutive 21 days. After completion of 4 cycles of chemotherapy, she had complaints of backache for the past 1 month, fever with productive cough since 4–5 days, and vomiting since 2 days. For her complaint, she visited a private practitioner in her locality, and her routine blood and urine investigation were done. On investigation, her random blood sugar (RBS) was found to be 338 mg/dL and postprandial blood glucose (PPBG) was 325.5 mg/dL. HbA1c was 12.4 and urine sugar was 3+. Liver function test (LFT) revealed raised values for serum glutamic-pyruvic transaminase (SGPT) (186 IU/L) and alkaline phosphatase (201 IU/L). Her complete blood count and ultrasonography abdomen were within normal limits. She was prescribed some medications, which she did not take. The following day, she presented with same complaint in the outpatient Department of Medicine, All India Institute of Medical Sciences, Jodhpur.

On detailed history, she informed that for the last 2 months she was also having increased frequency of micturition and excessive thirst. On examination, a healthy scar was present on the right breast. There were no other clinically relevant observations. Before first cycle of chemotherapy, her RBS (85.33 mg/dL) and SGPT (47.3 IU/L) values were within normal range. Moreover, she denies any history of diabetes mellitus in her family.

She was diagnosed as a case of uncontrolled diabetes mellitus for which she was prescribed Glycomet-GP1 (glimepiride 1 mg + metformin 500 mg) orally one tablet in the morning and Glycomet-GP2 (containing glimepiride 2 mg with metformin 500 mg) one tablet in the evening. Hydroxyzine 25 mg and paracetamol 500 mg were also added and were instructed to take as and when needed. A repeat request was sent for capillary blood sugar, RBS, PPBG, and LFT after taking medication for 2 weeks.

After 2 weeks of antidiabetic therapy in March 2016, her blood sugar was within the euglycemic range, i.e., fasting blood sugar and PPBG were 113 and 135 mg/dL, respectively.

DISCUSSION

Currently, three main groups of medications are used for breast cancer treatment, namely, hormone-blocking agents, chemotherapy, and monoclonal antibodies. Chemotherapy is usually given in combinations for periods of 3–6 months. They mostly work by destroying fast-growing or replicating cancer cells, either by causing DNA damage or by other mechanisms.[4,5]

Some breast cancers require estrogen (ER) for continued growth and express positive ER receptors on their surface. These ER receptors can be blocked by either tamoxifen or an aromatase inhibitor. Aromatase inhibitors are suitable for women after menopause as the enzyme is in active state mostly in the postmenopausal women.[7,8] EC regimen is used for breast cancer which is given for consecutive 21 days per cycle for 4–8 cycles.[9] The side effects of EC regimens are effects on the blood (such as risk of infection, anemia, bruising, and bleeding), hair loss (alopecia) or thinning, nausea and vomiting, mouth and dental problems, tiredness (fatigue), and effects on fertility.[10]

CY is a cytostatic drug widely used for the treatment of a number of neoplastic and inflammatory diseases.[11] To the best of our understanding and after thorough literature search, we could not identify any authenticated single case report of hyperglycemia with this regimen.

In autoimmune disease models such as experimental autoimmune encephalomyelitis and insulin-dependent diabetes mellitus, CY has been shown to promote susceptibility to the disease in nonobese mice.[12] It has been suggested that CY preferentially depletes regulatory (suppressor) cells.[13] The nature of these suppressors is largely unknown. There is growing evidence that Th2-like cells secreting interleukin (IL-4) and IL-10 provide protection, whereas pathogenic cells are Th1-like cell which secretes interferons alpha (IFN-α).[14] CY has been demonstrated to increases the number of IFN-α producer in the islet and renders these lymphocytes more pathogenic and capable of destroying the islets of pancreas.[15] Leukocytic infiltration of the pancreatic islets by autoimmune cells, or insulitis, can persist for long periods of time before the terminal destruction of β-cells. Analysis of cytokine secretion demonstrates that IFN-α producers are relatively resistant to the cytostatic action of CY and that a possible mechanism for this resistance may be a shift of individual Th0 clones toward the Th1 pathway. On the other hand, augmentation of the diabetogenic properties of the lymphocytes may not require a direct exposure of T cells to CY, suggesting a role for accessory cells in the acceleration of diabetes mellitus.[16]

The integrity of the immune system of breast cancer patients is severely affected by chemotherapy. Epirubicin causes increase in the counts of monocytes but decreased polymorphonuclear cells and lymphocytes. Percentages of T-cytotoxic cells and NK cells were increased, but the percentage of B-cells was dramatically decreased.[17] Thus, it is anticipated that epirubicin might have acted synergistically with CY in altering immune system. This possibly has contributed to the development of hyperglycemia in the index case.

Our patient developed symptoms of diabetes mellitus soon after completing four cycles of chemotherapy with EC. Although the pretreatment assessment of blood and urine sugar was within normal range, there is no family history of diabetes mellitus. Therefore, it seems likely that the chemotherapy-triggered immunological changes might have led to the new onset of diabetes mellitus.

In this case, the patient had improved gradually after starting the antidiabetic drugs. The patient is still continuing with her antidiabetic therapy. Considering all the factors on Naranjo's causality assessment algorithm, it is concluded that possible relationship exists between EC and this new onset diabetes mellitus.[18]

CONCLUSION

Caution is advised while administering these drugs in the form of repeat blood sugar examination to be done before every cycle of chemotherapy. On the other hand, alternative drug regimens may be tried that are better tolerated and are unlikely to be associated with such side effects.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. McGuire A, Brown JA, Malone C, McLaughlin R, Kerin MJ. Effects of age on the detection and management of breast cancer. Cancers (Basel) 2015;7:908-29.
2. Krishnan NM, Varghese C, Swaminathan R. Cancer: Current scenario, intervention strategies and projections for 2015. NCMH Background Papers·Burden of Disease in India; 2015. p. 219-25.
3. Holmes MD, Chen WY, Li L, Hertzmark E, Spiegelman D, Hankinson SE. Aspirin intake and survival after breast cancer. J Clin Oncol 2010;28:1467-72.
4. Damia G, D'Incalci M. Mechanisms of resistance to alkylating agents. Cytotechnology 1998;27:165-73.
5. Minotti G, Menna P, Salvatorelli E, Cairo G, Gianni L. Anthracyclines: Molecular advances and pharmacologic developments in antitumor activity and cardiotoxicity. Pharmacol Rev 2004;56:185-229.
6. Breast Cancer (Invasive) Treatment Regimens. Breast Cancer Advisor. Available from: http://www.cancertherapyadvisor.com/breast-cancer/breast-cancer-invasive-treatment-regimens/article/218154/. [Last cited on 2016 Apr 22].
7. Bao T, Rudek MA. The clinical pharmacology of anastrozole. Eur Oncol Haematol 2011;7:106-8.
8. Petit T, Dufour P, Tannock I. A critical evaluation of the role of aromatase inhibitors as adjuvant therapy for postmenopausal women with breast cancer. Endocr Relat Cancer 2011;18:R79-89.
9. Piccart MJ, Di Leo A, Beauduin M, Vindevoghel A, Michel J, Focan C, *et al.* Phase III trial comparing two dose levels of epirubicin combined with cyclophosphamide with cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer. J Clin Oncol 2001;19:3103-10.
10. EC Chemotherapy. Breast Cancer Care. Available from: https://www.breastcancercare.org.uk/information-support/facing-breast-cancer/going-through-treatment-breast-cancer/chemotherapy/ec-chemotherapy. [Last cited on 2016 Apr 24].
11. Reinolds JE. Antineoplastic agents and immunosuppressants. In: Martindale. The Extra Pharmacopoeia. London: The Pharmaceutical Press; 1993.
12. Lando Z, Teitelbaum D, Arnon R. Effect of cyclophosphamide on suppressor cell activity in mice unresponsive to EAE. J Immunol 1979;123:2156-60.
13. Yasunami R, Bach JF. Anti-suppressor effect of cyclophosphamide on the development of spontaneous diabetes in NOD mice. Eur J Immunol 1988;18:481-4.
14. Rabinovitch A. Immunoregulatory and cytokine imbalances in the pathogenesis of IDDM. Therapeutic intervention by immunostimulation? Diabetes 1994;43:613-21.
15. Campbell IL, Kay TW, Oxbrow L, Harrison LC. Essential role for interferon-gamma and interleukin-6 in autoimmune insulin-dependent diabetes in NOD/Wehi mice. J Clin Invest 1991;87:739-42.
16. Ablamunits V, Quintana F, Reshef T, Elias D, Cohen IR. Acceleration of autoimmune diabetes by cyclophosphamide is associated with an enhanced IFN-ã secretion pathway. J Autoimmun 1999;13:383-92.
17. Wijayahadi N, Haron MR, Stanslas J, Yusuf Z. Changes in cellular immunity during chemotherapy for primary breast cancer with anthracycline regimens. J Chemother 2007;19:716-23.
18. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, *et al.* A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239-45.