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Case report

RADIATION AND CHEMOTHERAPY INDUCED SECONDARY LEUKEMIA IN A CASE TREATED FOR CARCINOMA CERVIX: A CASE REPORT

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ABSTRACT

Secondary leukemias are usually forms of leukemias which are developed due to therapy administered for a previous malignancy. Radiotherapy or chemotherapy induced leukemia is a complication which follows treatment of a different primary malignancy. A case of acute monoblastic leukemia following treatment of the invasive carcinoma cervix (treated by radiotherapy and chemotherapy) is reported. This secondary leukemia developed one year after treatment. This case is being presented due to its rarity.

Keywords: Acute monoblastic leukemia, Radiation, Chemotherapy induced leukemia, Carcinoma cervix, Pelvic radiation

INTRODUCTION

The term secondary leukemia is usually employed to indicate either leukemia arising from myelodysplasia or acute leukemia developing after exposure to environmental or therapeutic toxins or radiation (therapy related).[1] Cervical cancer patients, treated with radiation therapy have statistically significant risk of developing acute non lymphoblastic leukemia; approximately 1-9 years after radiotherapy.[2] Secondary acute myeloid leukaemia can occur following exposure to cytotoxic agent (e.g. Drugs, radiation and toxic chemicals) or as a subsequent event following another hematological disorder, usually myelodysplasia. The risk of developing a second malignancy is estimated to range from 8% to 12% in a 20 year period after diagnosis of the first cancer. [1]

CASE REPORT

A 65 years old female presented with a history of vaginal discharge of two months duration, in Oct 2010. Clinical examination reveals infiltrative growth involving both lips of the cervix. Histopathological examination of the cervical growth showed moderately differentiated squamous cell carcinoma. Clinical staging of this carcinoma cervix was IIIB. Routine hematological parameters were within normal limits. Patient received radiation therapy and chemotherapy for carcinoma cervix for a period of six weeks. She received external beam radiation to pelvis 50GY in 28 fractions along with brachytherapy for 6

weeks. She also received chemotherapy, Cisplatin 40mg/m^2 weekly for six weeks.

After one year of the above treatment, a patient again presented with complaints of back pain radiating to chest and the fatigue of fifteen days duration in Oct 2011 (Approximately one year after first diagnosis of cancer cervix). Routine hematological examination showed Hemoglobin: 9.9gm/dl, total leukocyte count: 27,000/ cumm. Differential count showed: Monoblast: 80%, Neutrophil: 10% and lymphocyte: 10%. Platelet count was 01 lacs/cumm. Peripheral blood smear showed features of acute monoblastic leukemia on Leishman's stain (Fig 1 and 2). Nonspecific esterase was positive indicating monoblastic differentiation (Fig 3 and 4) .She was diagnosed as a case of Acute Monoblastic Leukemia (M5a) after an approximate period of one year following the start of treatment for carcinoma cervix.

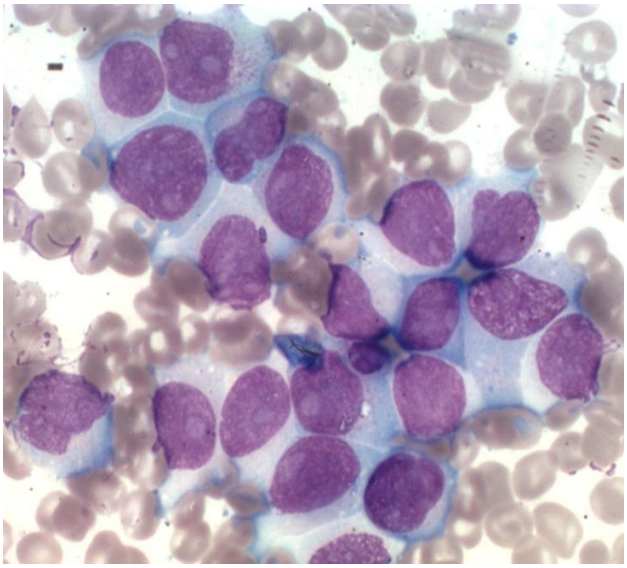

Fig1: Routine Leishman's stain (x 400)

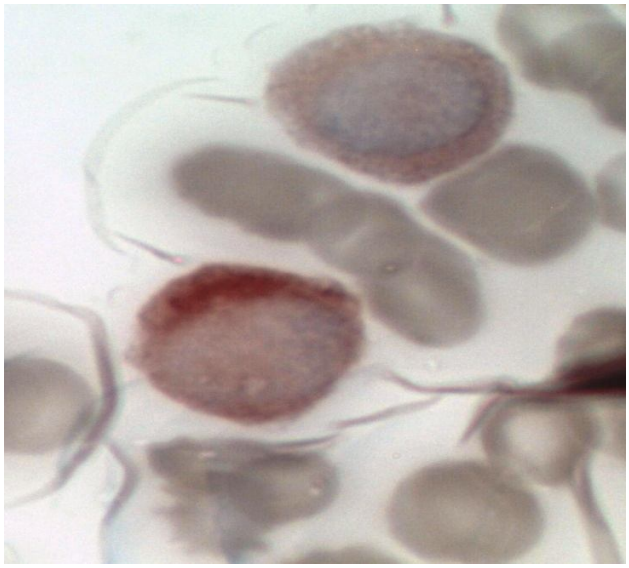

Fig 2: Special stain Nonspecific estarase (x 400)

DISCUSSION

Secondary leukemias usually result from chemotherapy for a different primary cancer but it also probably reflects an increased susceptibility to the cancer.[1] Therapy related acute non lymphoblastic leukemia and myelodydplasia are now recognized as the two most serious complications following the use of cytotoxic drugs. The major use of such drugs is in the treatment of malignant diseases. Development of secondary leukemia following high dose radiotherapy for primary cancer has been reported even after a period of more than 20 years after treatment.[3]

Secondary leukemia accounts for 10-30% of all acute myeloid leukemia (AML).[1] The majority of secondary leukemias result from the use of cytotoxic drugs bindings to the enzyme DNA topoisomerase. The risk of transforming acute myeloid leukaemia in women treated with alkylating agent is 7% at 10 yrs.[1]

Our patient developed acute monoblastic leukemia after completion of one year treatment for carcinoma cervix.(Combined radiotherapy and chemotherapy)

Therapy induced second malignant neoplasms occurs mainly due to the effects of ionizing radiation or chemotherapy or both. These agents induce non-lethal DNA damage to the bone marrow cells which subsequently undergo malignant transformation resulting in leukemia. Various chemotherapeutic drugs such as alkylating agents and platinum compounds are mutagenic in vitro and in laboratory animals.[4]

Carcinoma of the uterine cervix is the most common female genital malignancy in developing countries.[4] Majority of the patient present with

advanced disease. Cisplatin based concurrent chemo radiation is now the treatment of choice for this disease. Due to increased survival rates among such patients, treatment related second malignancy is also increasingly being recognized in these cases.[4]

Margaret A et al., and Chatuvediet. al., concluded that patients treated with radiotherapy for carcinoma cervix are at increased risk of developing a second cancer like that of the urinary bladder, ovaries, rectum, colon, female genital sites other than the cervix, bone and connective tissue. Following radiation therapy for both cervical and endometrial cancer, there is a small increased risk of developing leukemia.[2,5]

Following radiation therapy for cervical cancers there is a 20% increased risk of cancer developing close to or at an intermediate site, which may increase up to 40% if patient are followed up for a period of 10 years or more.[5] There is a 30% increased risk of developing acute non lymphoblastic leukemia.[5]

The risk of development of platinum induced leukemia depends on the cumulative dose of platinum administered. In multivariate analysis, the risk of developing acute myeloid leukemia was higher among patients whose initial management was with platinum based therapy than those undergoing radiotherapy alone.[4]

Platinum based chemotherapy of primary ovarian cancer increases risk of secondary leukemia. In a large study, 10,000 women with ovarian cancer, who were treated for six months with cumulative dose of platinum and followed up for a period of ten years, 71 cases developed leukemia. The cumulative dose of platinum was estimated to be 500 to 1000mg over a period of six months.[4,6]

Lois B et al, performed a study on patient of ovarian cancer and concluded that the risk of developing secondary leukemia was significantly increased after treatment with platinum based chemotherapy for primary ovarian cancer. They concluded that the magnitude of the risk was directly dependent on the cumulative dose of the drug as also the duration of the treatment. The risk of developing secondary leukemia was also significantly higher among the small number of patients who received both platinum and radiotherapy for primary carcinoma.[6]

Our patient received a cumulative dose of 300 mg of platinum together with radiation 50 GY infractions. Boice J D Jr.et. al., studied the relationship between dose and response of radiotherapy in 1, 50,000 women with invasive carcinoma of the uterine cervix. All of them received radiotherapy; of these 195 cases developed leukemia. They concluded that the risk of development of leukemia increased with increasing radiation dose to an average dose of about 400 rad was reached.[7]

Studies by MJ Ratain,et.al., on 119 patients of non-small cell carcinoma of the lung treated with combination chemotherapy cisplatin and other drugs, showed that four of these patients developed non lymphoblastic leukemia,1-4 years after the start of treatment.[8]

Of the 1, 99,268 patients of invasive tumor of vulva, cervix, uterus, anus and recto sigmoid junction who were treated with radiation and non radiation chemotherapy. Post treatment, risk of secondary leukemia peaked 5-10 years after primary treatment and remained elevated even 10-15 years after treatment. The conclusion was that pelvic radiation was associated with an increased risk of secondary leukemia.[9]

A population based cohort study on 18,657 patients with testicular cancer treated with radiotherapy without chemotherapy was associated with threefold elevated risk of leukemia. Radiation dose to active bone marrow and cumulative dose of cisplatin were both predictive of excess leukemia risk. The estimated relative risk of leukemia at cumulative dose of 650 mg cisplatin which is commonly administered in testicular cancer is higher. Larger doses of 1000mg are linked with statistically significant six fold increased risk.[10]

In one of the studies on 1,572 women treated with radiotherapy for cervical cancer and ovarian cancer, five of the patients developed non

lymphocytic leukemia. The author (Marushi I) concluded that there was a significantly increased risk of developing secondary leukemia in patients treated with large doses of radiation for other primary malignant neoplasms.[11]

Patients with secondary leukemias usually have an initial complete of remission rate over 50% of chemotherapy, but many of them may show relapse after varying intervals of time Despite intensive post-remission therapy only about 10% may be long-term survivors.[12]

CONCLUSION

A rare case of secondary leukemia (Acute Monoblastic leukemia) developing in a patient with primary squamous cell carcinoma of the cervix has been presented.

This case report and review of relevant literature shows that there is a high risk of developing a second cancer in the patient, treated for primary malignant neoplasm. This risk is dependent on the cumulative dose of both radiotherapy and chemotherapy. There is increased risk of secondary leukemia developing in patients of carcinoma of the cervix treated with radiotherapy and / or chemotherapy and this risk persists for about twenty years following the therapy. It is therefore recommended that patient of carcinoma cervix should with regular follow up for a period of least twenty years after completion of radiotherapy and/or chemotherapy.

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