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Therapy-Related Acute Myeloid Leukaemia Following Concurrent Radiotherapy and Chemotherapy for Humerus Angiosarcoma

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Abstract:

Concurrent chemo-radiotherapy has been an important part of angiosarcoma treatment. Its efficacy has been proven and its adverse effects are well understood. Leukaemogenesis is a potential late complication of ionizing radiation and chemotherapy and is thought to be a direct consequence of mutational events induced by previous therapy. Therapy-related acute myeloid leukaemia in angiosarcoma has rarely been reported in literature. We report a case of therapy related acute myeloid leukaemia in a 48 year old man, 2 years post chemo-radiotherapy for angiosarcoma of the left humerus. The aim of this study is to make physicians aware that this diagnosis should be considered in patients who survive a previous cancer and later presents with health problems.

Key words: Hemangiosarcoma, Radiation, Humerus, Acute Myeloid Leukemia, Neoplasms, Humans.

Introduction

Malignant vascular tumors of bone are very rare and accounts for less than 1% of primary malignant bone tumors. Angiosarcoma is an uncommon neoplasm characterized by rapidly proliferating and extensively infiltrating anaplastic cells derived from vessels and lining irregular, blood-filled spaces [1]. Age distribution shows a wide range from second to the eight decade of life [2]. Angiosarcomas tend to affect long tubular bones of the extremities and the axial skeleton, mainly the spine. Lower limb bones, femur and the tibia are commonly involved, followed by the pelvis, vertebral column and the bones of the upper limb [2,3]. The majority of patients require adjuvant chemo-radiotherapy with numerous courses upon subsequent relapses [4]. This prolonged use of chemo-radiotherapy increases the risk of therapy related secondary malignancy.

Case Report

A 48-year old Nigerian male had disarticulation of the left elbow joint in 2008 on account of osteosarcoma of the left ulna. Three years following surgery he noticed a painful mass in the left axilla. Excision of the mass was performed with clear margins. The histopathology report was consistent

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with angiosarcoma of the left humerus. Subsequently he received 6 cycles of chemotherapy consisting of paclitaxel (80 mg/m^2) and cisplatin (100 mg/m^2) and also 25 exposures of radiotherapy within a period of 6 months and 7 months respectively.

Two years post chemo-radiotherapy he was referred from a private hospital to our clinic on account of severe anemia. He had been transfused with 5 units of blood over a period of one month. Physical examination at presentation revealed a chronically ill-looking man, markedly pale and had bilateral pitting pedal-edema up to the distal 1/3 of the tibia. The musculo-skeletal examination revealed amputated left arm with septic ulcer in the lateral aspect of the axilla. Other systems were essentially normal. Presumptive diagnosis of chronic anemia secondary to chemo-radiotherapy and relapsed angiosarcoma of the left forearm with metastasis was made.

He was admitted and the following are results of investigations done: complete blood count (CBC) on admission; haematocrit 0.19 L/L, white cell count WBC 372×10^9/L, platelet Count 61×19^9/L, reticulocyte count 1.1%. The peripheral blood film (PBF) and bone marrow aspiration (BMA) cytology examination were in keeping with acute myeloid leukaemia - M2 subtype [Fig.1,2]. Myelogram was: myeloblast-35%, promyel-ocyte-20%, myelocyte-10%, metamyelocyte-8%, band forms-12%, matured neutrophils-8%, lymphoblast-2%, lymphocyte-05%. HB_SAg and anti-HCV antibodies screening were negative, HIV I & II were non-reactive. Other investigations carried out include: abdominal ultrasound scan revealed hepato-splenomegaly and enlarged kidneys. Liver function tests were essentially normal. Renal function tests revealed elevated creatinine and uric acid levels. Creatinine 118 µmol/L (53 -115 µmol/L), urea 4.8 mmol/L (2.1 - 7.1 mmol/L), uric acid 0.47 mmol/L (0.24 – 0.36 mmol/L).

Patient was duly counseled on the course and prognosis of the disease. Supportive therapy including blood products i.e. packed red blood cells and platelet concentrates, hydration and pre-chemotherapy medications were instituted. Definitive chemotherapy with doxorubicin 25 mg/ m^2 and cyarabinoside 100 mg/m^2 (DA Regimen) was commenced.

One day 2 of 1st cycle of chemotherapy patient vomited repeatedly and was hyperpyrexic, temperature ranging between 40.0^0C and 40.7^0C. A full septic work up was done and broad spectrum antibiotics (ceftriazone and metronidazole) were given. Unfortunately, the patient died three days after the commencement of chemotherapy.

Discussion

Angiosarcoma is an uncommon soft tissue sarcoma of endothelial origin that accounts for 1-2% of soft tissue sarcomas. These tumors represent a heterogeneous group of vascular neoplasms associated with aggressive clinical behaviors. They may originate in an anatomical site including deep soft tissue, breast, visceral organs and bone [5,6]. The tumors are frequently multifocal with insidious growth patterns which underlie the general adverse prognosis [5,6].

Angiosarcomas may develop spontaneously or following risk factors such as exposure to radiation, exogenous toxin such as vinyl chloride, thorium dioxide. Also, arsenic, radium and anabolic steroids have been associated with its development [7]. Upto 75% of cases relapsed mostly as local reoccurrences [8].

Wide local surgical resection is the corner stone of treatment, followed by systemic chemotherapeutic agents in majority of patients [9]. Radiotherapy and biological agents as adjuvant could also be used to decrease the risk of relapse.

Few retrospective studies as well as a prospective angiosarcoma multicenter phase II clinical trial suggest the possible efficacy of paclitaxel and/or cisplastin in the treatment of metastatic or locally advanced angiosarcoma [9]. These findings have led to a shift from the traditional doxorubicin based chemotherapy. Angiosarcomas are known to be sensitive to radiation, and may be used in conjunction with surgery when primary tumor cannot be completely resected [10].

Chemo-radiotherapy is not without side effects and patients are at increased risk of therapy related AML (t-AML). t-AML represents a unique clinical entity and carries a poorer prognosis than de-novo disease [11]. t-AML is thought to be due to the direct consequence of mutational events induced by cytotoxic drugs or radiotherapy. The latency between primary diagnosis and t-AML ranges between a few months to several years with a median of about 2 years, depending on the cumulative dose and/or the dose intensity of preceding chemotherapeutic agent. Alkylating agent–related AML typically develops after an average latency of 5-7 years [11]. Cisplatin, an alkylating agent is mutagenic in humans, producing intrastrand and interstrand DNA cross links. The persistence of DNA adducts in the bone marrow long after the completion of treatment also heightens the possibilities of late complications. The relative risk of developing cisplastin-induced leukaemia depends on the cumulative dose of the drug, length of the treatment and age of the patient [12]. Travis *et al*. [12], observed that the relative risk of AML in survivors of carcinoma of ovary treated with cisplatin-based chemotherapy was 1.9, 2.1, 4.1 and 7.6 when the cumulative dose of cisplatin was 500 mg, 500-749 mg, 750-999 mg and 1000 mg or more respectively. Radiation given concurrently with cisplatin also increases carcinogenic potential of the drug [12].

Several studies have shown that radiotherapy plays a significant role in the etiology of AML [12-13]. A cohort study analyzing chemical records of breast cancer patients with the aim of evaluating the long term effects of radiotherapy on the risk of second cancers reported a total of 389 (7.3%) malignancies in 5248 women [14]. Eight (0.15%) patients treated with radiotherapy developed leukaemia in the group as oppose to one case only in the group not receiving radiotherapy [14]. Taxanes such as paclitaxel also have leukaemogenic potentials. There are a few cases of t-AML related to pacitaxed exposure [15]. These leukaemias tend to be of aggressive sub-types with long latency periods. Our index patient had both of these chemotherapeutic agents as well as radiotherapy.

Monitoring of the short and long term outcomes of chemo-radiotherapy is warranted particularly with regards to development of secondary cancers. It also highlights the importance of assessing leukemia risk factors prior to commencement of these therapies.

Conclusion

The use of adjuvant chemo-radiotherapy in the management of patients with angiosarcoma to decrease the risk of relapse has a relatively modest survival gains. Premium should be placed on the planning of intensity of the chemotherapy, radiotherapy or combination of both in order to determine the optimal treatment in terms of efficacy and long term safety of treatment modalities.

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