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POST-IRRADIATION OSTEOSARCOMA OF THE ILIAC BONE: A CASE REPORT*

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The carcinogenic effect of ionizing radiation was recognized as early as a decade of its discovery[1-3]. Leukemia, lung cancer, thyroid cancer, and sarcomas of the bone and soft tissues are well documented examples of radiation-induced malignancies[4,5,6]. Following the advances made in the field of oncology, the incidence of secondary cancer has been rising parallel to the increase in the number of long-term survivors who received therapeutic irradiation[3,5,7]. It is reported that nearly 10-12 percent of long-term survivors may develop a second neoplasm, benign or malignant, within 30 years of the initial therapy[2,8,9].

One of the earliest recognized secondary malignancies to develop following radiotherapy given in the management of various disorders was sarcoma of bone; and such a case was first reported in 1922[6,10,11]. Since then, more than 250 cases of post-radiation sarcoma of bone have been reported[3]. Its incidence is reported to vary between 0.03% - 0.2%. These figures, though not very high, are considerably higher than the natural incidence of primary occurring sarcoma of bone which is estimated at five cases in every 100,000[4]. In a comprehensive study on the incidence of second primary tumors among childhood cancer survivors conducted by Hawkins et al[12], it was found that the relative risk of secondary malignant bone tumors associated with radiotherapy was about twenty-fold the expected number, and that they occurred mostly in the form of osteosarcoma. These serious sequelae gain further importance in pediatric age-group patients who are likely to live long after successful radiotherapy, chemotherapy or both.

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The following case of osteosarcoma of the right iliac bone in a child developing 12 years following the irradiation of an extensive retroperitoneal rhabdomyosarcoma is noteworthy because it developed in a long-term survivor of such a primary tumor. The tumor was confirmed both histologically and radiologically.

Case Report

A five-year-old girl was admitted to Hacettepe University Children's Hospital on January 6, 1975, with the complaint of abdominal pain of two months' duration. It was learned from her family that she had been operated on one month before for an abdominal mass detected on physical examination, without definite diagnosis.

Physical examination on admission revealed a slightly pale child who was in fair general condition. Her temperature was 36.5°C, pulse rate 124/min, and blood pressure reading 110/60 mmHg. The abdominal circumference measured 53 cm. She weighed 16 kg and her height was 103 cm. On abdominal palpation a mass of 29 × 15 cm was found on the right side of the abdomen which extended down to the pelvis. No other pathological findings were detected. Laboratory studies revealed a hemoglobin of 11.4 g/dl, white blood cell count of 6400/mm, normal differential count and urine examinations. Chest X-ray was normal. The IVP revealed a non-functioning right kidney with lateral displacement of the left ureter and indentation of the mass on the bladder. On January 7, 1975, the patient was operated on, and a hard, immobile mass was discovered in the right side of the abdominal cavity, almost occupying the entire abdomen, and fixed to the peritoneum, bowels and omentum. Only a biopsy could be taken, the microscopic examination of which revealed the diagnosis of embryonal rhabdomyosarcoma. According to these findings the patient was classified retrospectively as being in Stage III of the disease (Intergroup Rhabdomyosarcoma Study)[13]. A combined chemotherapy regimen of VAC (vincristine-i.v. actinomycin-D i.v. cyclophosphamide-p.o.)[14] was initiated post-operatively which was continued during and after radiotherapy. From January 16, 1975 to February 25, 1975, a total dose of 4500 cGy in 23 fractions was delivered to the tumour through adequate abdomino-pelvic anterior and posterior parallel opposed fields. The left kidney and the liver were protected in tolerance levels. By the termination of radiotherapy the mass reduced to 4 × 4 cm in size.

The patient did well in her follow-ups and continued chemotherapy regularly for a period of 22 months, till October 1976. Whereafter, she developed bouts of intermittent hematuria which after the necessary investigations was initially interpreted as benign recurrent hematuria. The cystoscopy performed in March 1981, revealed the diagnosis of hemorrhagic cystitis, probably related to cyclophosphamide. In August 1987, she returned to the hospital complaining of a recent painful swelling in the right hip following a traumatic event. On physical examination

there was a tender mass measuring 10 × 15 cm covering the right hip and extending into the pelvis. The roentgenograms of the pelvis showed an increased density of the right iliac bone with new bone formation extending to the adjacent soft tissues, and a "sun burst"-type periosteal reaction, suggesting osteosarcoma. The bone radionuclide scan revealed hyperactivity on the right innominate bone. Laboratory tests showed an elevated level of serum alkaline phosphatase of 232 IU. An open biopsy was taken from both the iliac bone and soft tissue which revealed the diagnosis of osteosarcoma. The patient was initiated on the T-10 chemotherapy protocol adopted by the Memorial Sloan-Kettering Cancer Center, starting with a high dose of 10 gm/m^2 of methotrexate[15]. Though surgical treatment was planned for the patient, this intervention was abandoned upon the detection of multiple pulmonary metastases in the thoracal CATs performed following the administration of six doses of methotrexate therapy. The treatment was continued with maintanance chemotherapy of the same regimen (cisplatin, adriamycin, bleomycin, cyclophosphamide, actinomycin D). An assessment made at the end of two courses showed no evidence of response in the metastatic disease, though there was a mild regression on the primary site.

In June 1988, the patient suffered a severe bout of hematuria which could not be controlled by conventional methods, and subsequently, a cystectomy was performed. The patient died on July 21, 1988, as a result of renal failure and septicemia besides advanced malignancy.

Discussion

Radiotherapy appears to be involved in the formation of many second primary tumors in childhood particularly after being used in treatment of retinoblastoma, central nervous system tumors, Wilms' tumor and Hodgkin's disease[2,5,8,12]. Secondary tumors following irradiation of soft tissue sarcomas are less frequent and sporadically reported[2,5,6,8,9,16]. Among the reported cases, the occurrence of osteosarcomas is even less. And as far as we could review the literature, we were able to detect only few cases of osteosarcoma following therapeutic irradiation for rhabdomyosarcoma[5,6,10,11]. This low incidence may be attributed to the relatively small number of long-term survivors among rhabdomyosarcoma patients for the present time.

The literature reports a wide range of radiation doses (1500-8500 cGy) which is complicated by osteosarcoma[5,8,12,16,17]. In the series reported by the Memorial Sloan-Kettering Cancer Center and the Mayo Clinic which comprises half the cumulative cases, the doses are above 2000 cGy[11].

The criteria for the diagnosis of post-irradiation osteosarcoma were established by Cahan et al in 1948[1]. They proposed that there should be no histologic or radiologic evidence of bone malignancy before irradiation, the secondary sarcoma

must arise within the radiotherapy field, there should be a latent period of a minimum of five years between radiotherapy and the clinical presentation of secondary sarcoma, and finally there must be histologic proof of the malignant tumor. Our case of osteosarcoma of the right iliac bone developing 12 years after therapeutic radiation for rhabdomyosarcoma with normal underlying bone, fulfills all the above-mentioned criteria.

Radiation-induced sarcomas of bone generally have a poor prognosis and the prognosis for sarcomas developing in the axial skeleton which are less commonly effected than long bones, is even worse[3]. In a series of 78 cases of post-irradiation osteosarcoma from the Mayo Clinic it was found that 30 percent of the patients with sarcomas of the extremities lived past the five-year survival rate without recurrence of disease, while none of the patients with sarcomas of the vertebra, pelvis and shoulder girdle did[10]. This difference in prognosis may be explained by the difficulty encountered in applying surgery, which is the primary treatment for osteosarcoma in these localizations. Our patient died of advanced local and metastatic disease only a few months after diagnosis. Our case coincides in this respect to similar cases reported in the literature[3,10]. The question remains as to whether or not the administered VAC combined chemotherapy played a role in the induction of osteosarcoma; as to our knowledge up until now no study has been reported to date regarding this.

It is worth mentioning here that the diagnosis of this rare but serious complication of radiotherapy should not outweigh its benefit in the management of cancer. It is of importance to keep this and other adverse effects in mind while planning radiotherapy, particularly in children with malignancies of long-term disease free expectation. It is also advantageous to remember that with recent advances made in the field of oncology, the relative incidence of treatment-related secondary malignancies will keep rising with life prolongation, therefore, a life-long follow-up seems to be necessary in children treated and cured of their primary cancer.

Summary

A case of osteosarcoma of the iliac bone developing 12 years after the successful management of childhood rhabdomyosarcoma is presented. The frequency of secondary tumors, mainly bone malignancies, following therapeutic irradiation in the pediatric age-group, and the criteria for the diagnosis of radiation-induced bone sarcoma are discussed.

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