Osteosarcoma as a Second Malignant Disease in a Case of Bilateral Retinoblastoma

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Abstract Patients with hereditary retinoblastoma, whether treated by radiation or not, are at an increased risk of subsequently developing sarcomas as a second malignancy. As the understanding of the underlying genetics of osteosarcoma and retinoblastoma has improved, a clear association between the two entities has been noted. We present a case of a young patient with previous history of bilateral retinoblastoma who was treated by surgery and chemoradiation for his primary disease and subsequent recurrences. Thirteen years after his initial diagnosis, he developed osteosarcoma of the mandible as the second primary lesion and was treated with surgery and chemotherapy. The intent of the case report is to bring forth the current thinking of genetic association between retinoblastoma and osteosarcoma and to discuss aggressive treatment protocol for the latter, in the form of surgery and chemotherapy.

Keywords Retinoblastoma · Osteosarcoma

Abbreviations

RIS Radiation induced sarcoma
OS-SMD Osteosarcoma as second malignant disease
Rb Retinoblastoma

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Introduction

Osteosarcoma of skull and mandible constitute about 10% of the total cases affecting axial and peripheral skeleton. It either arises de novo or can be predisposed by some underlying conditions like osteomyelitis, Li Fraumeni's cancer syndrome [1] and Paget's disease [2]. As increasing number of childhood malignancies are being treated by radiation, this ailment is now being increasingly seen as a radiation induced sarcoma (RIS). In fact, 63% percent of the total RIS are bony; osteosarcomas are most common, followed by malignant fibrous histiocytoma and fibrosarcoma [3].

Recently, the association between retinoblastoma (Rb) and osteosarcoma has emerged with the advent of new genetic information underlying these tumors. Patients with hereditary Rb, whether being treated by radiation or not, are at an increased risk of developing sarcomas as a second malignancy later in life [4]. We present a case of osteosarcoma developing in a patient with Rb and discuss the pertinent issues regarding management of osteosarcoma as a second malignant disease (OS-SMD).

Case Report

A 19-year-old male presented to the outpatient department of this institute with complaints of a swelling in the right parotid area and decreased mouth opening for a duration of 10 months.

Previously, at six years of age, he was diagnosed to have Rb of the right eye with extension beyond the globe. A contrast enhanced CT scan of the orbit showed intraocular soft tissue mass on the right side with areas of calcification within (Fig. 1). He underwent enucleation of right orbit followed by chemoradiation. A total of 45 Gy was

Fig. 1 Axial contrast enhanced CT of orbit showing an enhancing intraocular mass in the right globe with calcification

administered along with five cycles of chemotherapy. A year later he was diagnosed to have an early lesion of Rb in the left eye for which he was successfully managed by laser and cryosurgery.

At the age of 14 years he presented again, this time with a swelling in the right preauricular region with an aspiration cytology suggesting metastatic Rb. He was managed this time with 20 Gy of external beam radiation and six cycles of chemotherapy (VAC regimen- Vincristine, Adriamycin, Cyclophosphamide) to which he favorably responded with complete ablation of disease. There was a second recurrence in the same region at 17 years of age. Aspiration cytology again suggested Rb and a PET scan showed increased uptake in the mass at the ascending ramus of the right mandible. Patient again responded to six cycles of chemotherapy (VAC+ICE- Vincristine, Adriamycin, Cyclophosphamide + Ifosfamide, Carboplatin, Etoposide).

Fig. 2 Axial contrast enhanced CT of the neck showing bony destruction of right mandibular rams associated with a soft tissue mass in the masseter space and parapharyngeal space with osteoid new bone formation. (**a** soft tissue window, **b** bone window)

On this visit, he had a firm swelling in the right parotid area with decreased mouth opening. There were no palpable cervical nodes and an intraoral examination could not be carried out due to trismus. A contrast enhanced CT scan of the neck showed lytic destruction of the right mandibular ramus with large soft tissue mass infiltrating into the masseter and the pterygoid muscles with areas of osteoid new bone (Fig. 2).

Aspiration cytology showed features of pleomorphic sarcoma. However, as the imaging features were suggestive of osteosarcoma he was taken up for surgery after two cycles of chemotherapy with methotrexate. Patient underwent right hemimandibulectomy, right supraomohyoid neck dissection and infra-temporal fossa clearance. Grossly, the tumor involved the vertical ramus, angle of the mandible and posterior part of the horizontal ramus. It had also infiltrated the masseter and the pterygoid muscles and the facial nerve. All the involved structures were resected. Postoperative histopathology was suggestive of osteosarcoma, predominantly of fibroblastic and cartilaginous differentiation with foci of osteoid formation. There was involvement of pterygoid muscles that were resected as separate posterior margin. The postoperative period was uneventful and he was administered postoperative chemotherapy three cycles (ifosfamide, cisplatin and high-dose methotrexate). A post operative PET scan was carried out at four months after surgery that showed no abnormal uptake at the site of disease or anywhere else in the body. The patient is doing well with no evidence of loco-regional or metastatic disease at six months of follow-up.

Discussion

The mutations seen in the genome of patients with bilateral Rb and those with osteosarcoma are sometimes common, involving Rb gene and also affecting p53 tumor suppressor

gene [5]. For this reason, there is increased propensity of cases with bilateral Rb to subsequently develop OS-SMD.

However, osteosarcoma is also commonly seen as RIS. Cahan et al. [6] had mentioned four criteria for tumors to be classified as RIS. (1) radiation must have been delivered to the site in question, (2) the new malignancy must arise within the irradiated field, (3) the new tumor must be histologically distinct from the original primary lesion, and (4) a latent period between the time of radiation exposure and development of the new malignancy must be several years. Though the threshold for development of RIS has not been described but its risk tends to increase with increasing radiation dose [4].

While the treatment of primary osteosarcoma has been on clearly defined protocol of surgery and chemoradiation, that of OS-SMD had not been well established. Traditionally, the prognosis of patients with secondary bone sarcomas has been considered to be poor [7]. However, few recent reports have shown significant improvement in actuarial and disease free survival with aggressive management of OS-SMD [8, 9]. Osteosarcoma of head and neck as such shows poorer results than that of extremities due to proximity to skull base and great vessels, and difficulty in getting a negative margin. Certain prognostic factors have been mentioned in relation to OS-SMD like, site of disease, response to preoperative chemotherapy and surgery with wide margin [8]. While few authors feel that histology of previously treated malignancy influences prognosis [8], others don't agree [4]. However, variables including the initial age at radiotherapy, primary site, total radiation dose and latency period have no significant effect on survival [4].

In the present case, the patient developed osteosarcoma of the mandible as a second malignancy after the treatment of recurrent bilateral Rb. The entity meets all the criteria of being classified as a radiation induced malignancy. However, the patient was also predisposed to developing osteosarcoma due to previous history of bilateral Rb. The disease extended close to the skull base and involved infratemporal fossa; hence it could not be excised with a

wide margin all around. An aggressive postoperative chemotherapy was instituted. The patient is under close follow up and remains disease free at six months of follow up.

The incidence of OS-SMD is likely to increase with improved survival in patients with head and neck cancer and better treatment protocols for patients with bilateral Rb. Though radiology is helpful in diagnosis and planning of the treatment, the imaging findings are not pathognomic of the same [3]. The treatment of OS-SMD can be best addressed by radical surgery and aggressive preoperative and postoperative chemotherapy.

Conflict of interest None.

Reference

1. Varley JM, Evans DG, Birch JM (1997) Li-Fraumeni syndrome a molecular and clinical review. *Br J Cancer* 76:1–14
2. Wick MR, Siegal GP, Unni KK, McLeod RA, Greditzer HG III (1981) Sarcomas of bone complicating osteitis deformans (Paget's disease): fifty years' experience. *Am J Surg Pathol* 5:47–59
3. Sheppard DG, Libshitz HI (2001) Post-radiation sarcomas: a review of the clinical and imaging features in 63 cases. *Clin Radiol* 56:22–29
4. Koshy M, Paulino AC, Mai WY, Teh BS (2005) Radiation-induced osteosarcomas in the pediatric population. *Int J Radiat Oncol Biol Phys* 63:1169–1174
5. Miller CW, Aslo A, Won A, Tan M, Lampkin B, Koeffler HP (1996) Alterations of the p53, Rb and MDM2 genes in osteosarcoma. *J Cancer Res Clin Oncol* 122:559–565
6. Cahan WG, Woodard HQ, Higinbotham NL et al (1948) Sarcoma arising in irradiated bone: report of 11 cases. *Cancer* 1:3–29
7. Huvo AG (1991) Bone tumors diagnosis, treatment, and prognosis, 2nd edn. W.B. Saunders, Philadelphia
8. Bielack SS, Kempf-Bielack B, Heise U, Schwenzer D, Winkler K (1999) Combined modality treatment for osteosarcoma occurring as a second malignant disease. Cooperative German-Austrian-Swiss Osteosarcoma Study Group. *J Clin Oncol* 17:1164–1174
9. Tabone MD, Terrier P, Pacquement H, Brunat-Mentigny M, Schmitt C, Babin-Boilletot A et al (1999) Outcome of radiation-related osteosarcoma after treatment of childhood and adolescent cancer: a study of 23 cases. *J Clin Oncol* 17:2789–2795