REPORTS OF PRACTICAL ONCOLOGY AND RADIOTHERAPY 23 (2018) 266–269

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Case report

Central nervous system metastasis from osteosarcoma: Case report and literature review

María Tereza Nieto-Coronel[a,c,*], *Allan David López-Vásquez*[a,c], *Diana Marroquín-Flores*[a,c], *Sandy Ruiz-Cruz*[a,c], *Jorge Luis Martínez-Tláhuel*[a,b], *Jaime De la Garza-Salazar*[a,b]

[a] *National Cancer Institute, Mexico City, Mexico*
[b] *Medical Oncologist-Medical Oncology Department, Mexico*
[c] *Resident – Medical Oncology Department, Mexico*

ARTICLE INFO

Article history:
Received 23 October 2017
Received in revised form
22 February 2018
Accepted 23 June 2018
Available online 26 July 2018

Keywords:
Osteosarcoma
Brain metastasis
Radiation therapy

ABSTRACT

Osteosarcoma is the most common primary malignancy of bone in children and young adults, the highest incidence peak is during adolescence and doesn't have any gender predominance. The main site of metastasis are the lungs and extrapulmonary cases are occasional. The incidence of metastasis in the Central Nervous System (CNS) is 2–6.5%, increase to 10–15% in patients with pulmonary metastases. Therefore, metastatic disease of the CNS is rare and the information on such patients is limited. Here, we describe a case of a 20-year old patient diagnosed with osteosarcoma in the left distal femur stage IIB, he developed pulmonary disease, during palliative chemotherapy experienced relapse to the brain classified as *recursive partitioning analysis* (RPA) class II, and was treated with external radiotherapy (30 Gy in 10 fractions) and later he had a poor evolution and died.

1. Introduction

Osteosarcoma is a malignant primary bone tumor caused by the production of osteoid material by malignant cells; it is a rare neoplasm [1]. Osteosarcoma represents 4.5% of the total neoplasms in pediatric populations in Mexico City [2]; other age group affected (albeit notably less) are older adults over 80 years with a previous history of radiotherapy [3]; regarding incidence, there are no racial or gender differences. Younger patients and lesions located in extremities rather than in the pelvis or spine have better prognosis [1].

Many patients with osteosarcoma, particularly children, have a genetic predisposition, with Rb1 gene mutation (related to hereditary retinoblastoma) and p53 mutation (related to Li-Fraumeni syndrome) being the most frequent ones [4]. In adult cases, the main risk factor is radiotherapy, with an interval between irradiation and the appearance of osteosarcoma ranging from 12 to 16 years [5], another risk factor is Paget's disease [6].

* Corresponding author at: 22 San Fernando Avenue, Sección XVI, Tlalpan, Mexico City 14080, Mexico.
E-mail address: maytemtnc2@gmail.com (M.T. Nieto-Coronel).
https://doi.org/10.1016/j.rpor.2018.06.003

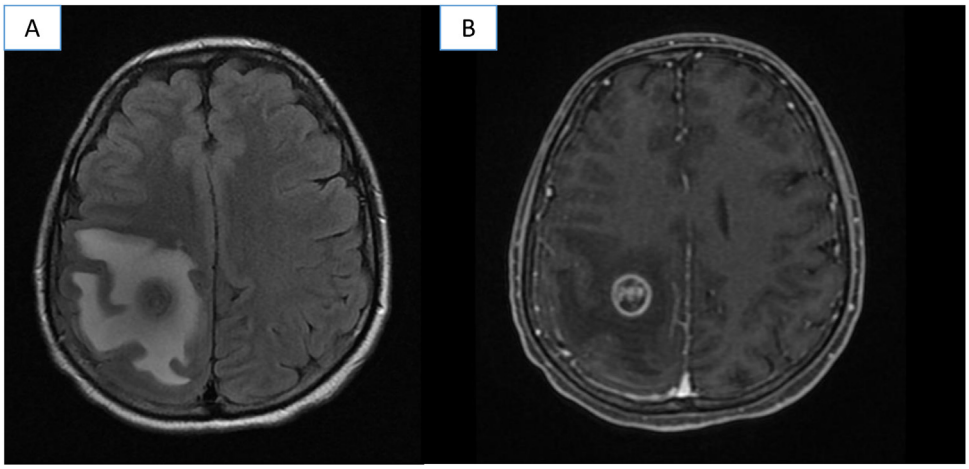

Fig. 1 – MRI with right frontoparietal lesion with perilesional edema: A. T2 FLAIR sequence B. With gadolinium.

Previous to the advent of chemotherapy, patients were treated with surgery and/or radiotherapy and developed metastasis in 80% of cases. Adjuvant chemotherapy currently used in the treatment has been demonstrated to increase overall survival from 16% to 70% [7]. The main site of metastasis is the lungs (40% at diagnosis), extrapulmonary metastasis are rare and curable in less than 5% of patients [8,9]; the incidence of CNS metastasis is 2–6.5% [9,10], in patients with a pulmonary metastases it increases to 10–15%, but these are rarely symptomatic by themselves at diagnosis [11,12].

Metastasis to CNS is rare, but this may be changing with overall survival improvement in the modern chemotherapy era [13,14], we present a patient diagnosed with metastatic osteosarcoma to the lungs, that developed metastasis to the CNS during palliative treatment with chemotherapy.

1.1. *Case presentation*

20-Year old male was diagnosed with osteoblastic osteosarcoma of left distal femur stage IIB (T2, G2, N0, M0), he received three cycles of platinum-based neoadjuvant chemotherapy and subsequent supracondylar amputation, hystolopathologyical report was Huvos IIA. One month after surgery, he developed lung metastasis. Palliative treatment with Docetaxel (75 mg/m^2 D1) and Gemcitabine (1000 mg/m^2 D1 and D8) for three cycles was started. Later, he was admitted to the emergency room for left body hemiparesis and sudden holocraneal cephalea with 24 h of evolution. Motor examination revealed left paresis (power left upper limb and left lower limb 3/5) and osteo-tendinous reflexes ++. He was further evaluated with computed tomography (CT) which revealed a right fronto-parietal lesion with perilesional edema. Brain magnetic resonance imaging (MRI) showed a fronto-parietal lesion hypointense on T1, heterogeneous on T2, reinforced in a ring shape with contrast, and perilesional edema in FLAIR sequence (Fig. 1). The patient was classified as RPA class II (for extracranial metastasis) and received external holocraneal radiotherapy 30 Gy in 10 fractions, showing clinical improvement. Afterwards, he was subjected to right posterolateral thoracotomy with resection of six pulmonary lesions and started treatment with Ifosfamide/Etoposide for one cycle, which caused hematological toxicity grade 4, hypovolemic shock for hemoptysis and the deterioration of the performance status. After this event, the patient remained with palliative care equipment and died 14 months after diagnosis.

2. Discussion

Metastases to CNS in osteosarcoma patients are rare [10], we collected information of all cases reported in the literature, we searched in Pubmed/MEDLINE and Google Scholar with the keywords “Osteosarcoma” AND “brain metastasis” OR “CNS metastasis”, exclusion criteria were: no complete information and brain primary, we found 35 cases and seven were excluded. 28 cases were evaluated in the literature and our case. Table 1 shows the characteristics of those patients.

Median age was 15.72 years (3–36 years), 37.9% were females, the most frequent primary site was femur (58.1%), 70.3% (23 patients) were diagnosed for local disease and six (20.68%) for metastatic disease, treatment was heterogeneous, with only four (13.79%) patients treated with neoadjuvant chemotherapy; 75.86% of patients who developed brain metastases had lung metastasis, median time to brain metastasis was 26.60 months (4–84), eight patients were treated with surgery ± radiotherapy, eight patients with chemotherapy ± radiotherapy, one patient with radiotherapy only, and eleven patients did not receive any treatment, median overall survival was 32.12 months(4–120).

More cases have been described with the introduction of chemotherapy [14,19], Marina et al. described 254 patients with osteosarcoma, 13 with brain metastasis, showing that patients diagnosed after 1982 (advent of chemotherapy) have an increased risk of brain metastasis ($p = 0.007$), but not with a different frequency (15.5% vs. 4.5% $p = 0.125$) [10]. In our analysis 15 patients (51.72%) received chemotherapy and two were included in the MIOS trial.

The dissemination route is presumably hematogenous, through lung metastases [19]. It has been described that brain lesions caused by osteosarcoma are hypervascularized and mimic multiform glioblastoma [11]. Generally, they are located in the cerebral cortex, although some cases in the cerebellum

Table 1 – Clinical characteristics, treatment and outcome of patients with brain metastases.

Year	Author	Age	Gender	Primary site	Initial clinical stage	Initial treatmetnt	Other sites of metastases	Time to brain relapse (mo)	Treatment to brain metastases	Overall survival (mo)
1979	Danziger [12]	20	F	Right distal femur	Metastasic	–	No	Initially	CT, RT	ND
1979	Danziger [12]	15	F	Right distal femur	Locally	CT, RT, surgery	Lung, bone	24	Surgery	33
1979	Danziger [12]	18	F	Distal femur	Metastasic	–	Lung, breast	6	CT, RT	6
1983	Ozarda [15]	23	M	Rigth femur	Localy	ND	No	8	CT, RT	ND
1990	Niedeggen [16]	7	M	Left femur	Locally	Surgery, CT	Lung	76	Surgery, RT	13
1993	Marina [10]	3	M	Left upper humerus	Locally	Surgery	Lung	4	CT	4
1993	Marina [10]	10	F	Left distal femur	Locally	Surgery	Lung, bone	20	None	20
1993	Marina [10]	25	M	Proximal tibia	Locally	Surgery	Lung, bone	38	None	38
1993	Marina [10]	12	M	Left distal femur	Locally	CT	Lung	14	None	14
1993	Marina [10]	15	M	Left proximal humerus	Locally	Surgery	Lung	11	None	12
1993	Marina [10]	18	M	Left distal femur	Locally	Surgery	Lung	41	None	41
1993	Marina [10]	9	M	Rigth proximal humerus	Locally	Surgery, CT	Lung	15	None	16
1993	Marina [10]	4	M	Left proximal humerus	Locally	Surgery	Lung	10	CT	103 (NED)
1993	Marina [10]	19	F	Left proximal tibia	Locally	Surgery, MIOS	Lung	45	CT	47
1993	Marina [10]	17	M	Left proximal femur	Locally	Surgery, MIOS	Lung	15	None	16
1993	Marina [10]	19	M	Left distal femur	Locally	Surgery, CT	Lung, local	12	None	12
1993	Marina [10]	7	F	Right distal femur	Locally	Surgery, CT	Lung, local	18	None	18
1993	Marina [10]	17	M	Distal humerus	Locally	Surgery, CT	Local	8	None	8
1993	Marina [10]	16	M	Distal femur	Locally	Surgery, CT	Lung, local	12	None	15
1993	Wexler [13]	10	F	Neck of right femur	Locally	Surgery, CT	Lung	53	Surgery. RT	120
1994	Chang [17]	20	M	Bilateral femur	Metastasic	–	ND	Inically	Surgery, RT	5
2002	Hettmer [18]	16	M	Left proximal tibia	Locally	CT, surgery	Lung	84	CT	84
2003	Yonemoto [19]	14	F	ND	Locally	CT, surgery	Lung	12	Surgery, RT	114
2005	Weil [20]	26	M	Rigth tibia	Metastasic	CT, surgery	Lung	36	Surgery, CT, RT	4
2009	Niazi [11]	16	M	Metaphysis of the rigth femur	Metastasic	ND	ND	Initially	ND	ND
2012	Onodena [21]	14	F	Left femur	Locally	Surgery, CT	No	12	Surgery	ND
2013	Rabah [22]	10	F	Right humerus	Metastasic	–	No	Initially	CT, RT	14
2017	Doval [23]	36	F	Left femur	Locally	Surgery, CT	Lung	84	Surgery	ND
2018	Present case	20	M	Left distal femur	Locally	CT, surgery	Lung	7	RT	14

F: Female, M: Male, ND: No data, mo: months, CT: Chemotherapy, RT: Radiotherapy, MIOS: Multi-institutional Osteosarcoma study, NED: No evidence of disease.

have also been reported [18,24]. In the patient described in this case, metastases were found in the right frontoparietal region of the cerebral cortex.

Baram et al. presented 87 patients with osteosarcoma, 39 of them had pulmonary metastases and five with brain metastases; clinical manifestations were catastrophic: two with massive hemorrhages and three with epileptic status [9]; we described the patient with hemiparesis and cephalea.

Approximately 30–40% of patients with localized tumors develop lung metastasis and 10–15% of those patients experienced relapse, they may be at risk of brain metastasis [18], we found 75.86% of patients with lung metastases.

Baram et.al. found two patients (2/5) with brain metastases and both had surgery with a transient clinical improvement [9], lesions potentially treatable with surgery are single lesions, long survival has been reported only in isolated cases [16,18]. We found only eight (27.58%) patients treated with surgery ± radiotherapy with a median overall survival of 48.16 months.

The prognosis of patients with intracranial metastasis is poor, mean interval to brain metastases from initial diagnosis is approximately 20 months in soft tissue sarcomas and survival is no longer than several months [18,25], we reported a median time to brain relapse of 24.51 months and overall survival was 32.1.

3. Conclusion

Brain metastasis is an unusual event in osteosarcoma, currently there is no accurate information on the incidence of this complication, as we previously mentioned, there are case reports of this complication with different experiences in clinical management. The prognosis of these patients is very poor, we reported. Some authors suggest periodical neuroimaging studies in patients with lung metastatic disease, although this statement is controversial.

Financial disclosure

None declared.

Conflict of interest

None declared.

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