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A Rare Case of Synchronous Metastasis of Osteosarcoma: Need for Clinical Risk Factors Analysis

Subbiah Paulraj[1]* and K Ramalingam[2]

[1]*Executive Chairman, Advanced Centre for Conservation Education, CSPT, Guindy, Chennai, Tamil Nadu, India , Pin code: 600022*

[2]*Scientist, Mediclone Research Center, Mediclone Biotech coy, Chennai, India , , Pin code: 600048*

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***Corresponding author:** Dr.S. Paulraj, Executive Chairman, ACCEPT, Chennai Snake Park Trust, Guindy, Chennai, India , Pin code: 600022
Email: paulrajifs@gmail.com

Abstract

Osteosarcoma is a rare condition with a complex treatment commonly reported in teen age children. With the present standard treatment protocols, one could achieve up to 76% overall survival rate in any case of localized osteosarcoma. However, the risk factors involved in the 24% failure cases in such treatments are not properly addressed although many research findings provide systematic interventions for the same. In the present case study, the possible influence of various clinical risk factors that adversely influenced failure in the present treatment protocol for the localised osteosarcoma and the availability of various mitigating measures for reducing their adverse impacts are analyzed and discussed in the light of various research findings.

Keywords: Osteosarcoma; Biopsy; Surgery; Chemotherapy; Risk Factors; Synchronous Metastasis

Introduction

Osteosarcoma is commonly reported in teen age children. The standard treatment protocols include neoadjuvant chemotherapy, surgery, and consolidation chemotherapy [1]. The 5-year relative survival rate for people of all ages is 76%, if osteosarcoma is diagnosed and treated before it has spread outside the area where it started [2]. In recent years, novel insights have been offered towards reducing the deficiency gap of 24% recognizing the risk factors involved in the deficiencies in the osteosarcoma treatment [3]. The risk factors include inadequate competency of the doctors and the hospitals which are involved in the treatment protocol [4,5] methods of biopsy [5-10] surgical injury [11-13] and therapeutic protocols [14]. Normally, in the case of a localised osteosarcoma treated with conventional chemotherapy and surgery, the mean time to the first relapse (metachronous) is greater than 18 months [15]. In contrast to this contention, report presents a case of a girl patient who died within a short period, possibly ignoring the clinical risks in treatment of her highly localised osteosarcoma. It is clarified that such clinical risks originate because of defects in the in-depth knowledge of the clinicians on the impact of surgical injuries and insufficiencies in the healthcare system [16]. To eliminate such defects, systematic interventions should be implemented to control the risks to protect the patients from risks [17,18]. The objective of this case study is to expose the clinical risk factors involved in such aggressive metastasis (synchronous) based on the new findings on the advancements made on the risk factors. Such exposure of the deficiency may contribute to improving in the survival rate of the children newly afflicted with osteosarcoma and highlight the need to modify clinical management strategies in the prognosis of any complicated disease as critically analyzed by Farokhzadian et. al [19].

Case Report

A girl patient, aged 11, with persistent right leg knee pain existing over a period of six months, was referred to a reputed orthopaedic hospital in Chennai, in the state of Tamil Nadu, India. The findings of 3 Telsa-MRI report dated 29th Sep. 2021 revealed the following features: (a) A large expansile lesion (measuring 14.0x6.2 cm) involving Meta diaphysis of right distal femur with extension into epiphysis; (b) The lesion showed osteoid matrix mineralization with sun burst periosteal reaction and Codman's triangle formation; (c) No evidence of intra articular extension

was noticed; (d) ACL, PCL and both menisci appeared normal; and (e) No evidence of lung / mediastinal secondaries noticed. Based on these findings, the presence of osteosarcoma of right distal femur was concluded. Based on the MRI report, a well-known senior orthopaedic surgeon of the hospital independently decided to perform an open biopsy, and he performed the same on 2nd Oct. 2022. The biopsy specimen was examined in a reputed city hospital lab. The case summary revealed features suggestive of osteosarcoma. Further details included Tumor location: Metaphysis; Histological type: Osteogenic tumor – conventional osteosarcoma with histological grade: G3 poorly differentiated; Mitotic rate: 50 per 10 HPF; Necrosis present 15%; Lymph vascular invasion: Not identified.

The patient was advised to go for two cycles of preoperative chemotherapy before the proposed limb salvage surgery. Accordingly, the patient underwent the first cycle of chemotherapy from 15th October and the second cycle from 6th November 2022. The conventional Cisplatin chemo drug was used in both cycles.

As the biopsy surgery injury site was not properly healing and abnormal swelling of the surgical site with pain was experienced, the patient was referred for investigation on 28th November. After examining the prognosis, it was decided to advance the proposed limb salvage surgery and the same was performed on 30th November as follows: Wide resection and CMP replacement dist. Femur implanted with titanium femur lengthening prosthesis. After surgery, the resected specimen right distal femur with attached all around soft tissue and a portion of tibia was sent for cell culture and histopathological test to a reputed lab. on the same day as surgery. The following is the summary of the impression report dated, 15th December: Tumer location and extant: Metaphysis extending to epiphysis and diaphysis; Tumer size: 12.5 x 8.5 x 6 cm: Histologic grade: G3 poorly differentiated high grade; Mitotic rate: 20/10 HPF; Necrosis: Present; Treatment effect: Present; Extent of treatment effect: 38%; Lymph vascular invasion: present; Proximal scoop margin, soft tissue and skin resection margins: uninvolved by sarcoma; pathological stage classification (PTNM, AJCC 8TH EDITION): ypT3; Tibia with soft tissue: Negative for tumour infiltration. The patient was advised for post- operative chemo treatment. But it was not done due to severe side effects of the past chemotherapy treatments. The patient underwent dental surgery for inflammation at the new tooth eruption site during mid-December 2022. However, the inflammation reappeared in the same site and persisted. (later report confirmed that it was due to metastasis and spread of tumour to Jaw bones). As the patient felt severe back ache radiating to bilateral legs for a week, she was referred to a surgical oncologist on 3rd January 2023, who recommended for a PET scan report for taking up further treatment. The PET scan was performed on 5th January; the report revealed a shocking observation of severe metastasis spreading to various body parts, revealing axial and appendicular skeletal metastasis, nodal metastasis, pulmonary metastasis, metastatic deposits in muscles of right thigh and left side mandible. After observing the aggressive cancer spreading based on the PET scan report, the medical oncologists were reluctant to go for further treatments involving Chemo or radiotherapies and suggested for a palliative care, normally recommended for any final stage cancer patients. The patient died after two months under palliative care on 24th March 2022 without opting for any curative treatments.

Discussion

The above case raises the following questions. i. Although the osteosarcoma is said to be an aggressive cancer, recent treatment protocol provides opportunities for 70 to 80 % DFS rates for any localised osteosarcoma, what clinical factors influenced the synchronous metastasis after the treatment started. ii. Role of tumour seeding due to biopsy in local metastasis, iii. Role of major surgical injury in influencing local organ metastasis, iv. Role of medication such as chemotherapy / radiotherapy in local organ metastasis. Earlier case studies on osteosarcoma may through light on answering the above questions.

Metastasis rate of primary osteosarcoma after starting the treatment

In this present case the metastasis to local organs started within three months (synchronous) from the start of the treatment from the localized primary site. Jeffree et.al. reported that, the first organ affected by osteosarcoma from the primary site was the lungs and the median time for this metastasis was 5-6 months after starting treatment; in many cases metastases were observed between 1and 6 months, indicating that, the patients were liable for synchronous metastasis even after one month from the date of commencement of treatment [5]. This observation supports the fact that osteosarcoma is capable of metastasizing even after a month of treatment started. But the risk factors involved in such early and vigorous metastasis were not analyzed by these authors.

Risk of Biopsy seeding for local metastasis

Although biopsy is a crucial step in the management of musculoskeletal sarcoma, poorly performed biopsies and complications of biopsy procedure can considerably compromise subsequent management of the tumour [6-8]. Barrientos-Ruiz et al. in their detailed comparative study on the Seeding of Biopsy tracts of the osteosarcoma patients concluded that open biopsies were associated with an increased risk of tumoral seeding of the biopsy site, and tumoral seeding was associated with an increased risk of local recurrence [9]. Cannon and Dyson reported that 5 out of 13 (38%) patients, on whom the open biopsy scar could not be excised en block with the tumour, had local recurrence following resection and prosthetic replacement for malignant bone tumours. The above observations are clear evidence to say that open biopsy has a greater risk for tumour seeding [6-10].

Risk of Major injuries inflicting tumour metastasis

Demicheli et. al. has given a historical perspective of various reports supporting surgery induced tumour growth

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and metastasis [11]. However, such reports had generally been dismissed as anecdotal until more recent evidence demonstrated that the surgical operation may generate a permissive environment for tumour growth [12]. Alieva et. al. in their recent review summarized the current literature regarding local, systemic, and secondary side effects of surgical interventions on tumor progression and dissemination. He brought out evidence suggesting that even minor surgical trauma can influence physiological process that might promote post operative metastatic spread and tumor recurrence [13].

Risk of medication on tumor spreading

A body of evidence presented over the past several years indicates that chemotherapy treatments favor cancer cell dissemination. If chemotherapy is given pre-operatively, significant changes occur in the composition of the primary tumor microenvironment which may favor the metastasis-promoting rather than the metastasis–suppressing components of the tumor microenvironment [14]. They categorically analyzed Chemotherapy-induced systemic and tissue-specific pro-metastatic effects with supportive research findings as follows: Chemotherapy may provide systemic support for metastasis through the induction of pro-inflammatory circuits; mediates the mobilization of bone marrow progenitors to primary and secondary sites to promote metastasis; May promote EMT and increased cancer cell invasiveness; May affect cancer cell intravasation and dissemination; May convey pro-metastatic properties on circulating tumor cells and Chemotherapy may facilitate cancer cell seeding and colonization at distant sites [14].

Interpretation of the findings with reference to the case study

In this case study, the reports of MRI, biopsy sample and tissue sample from resected tissue indicated that the tumour was localized and not metastasized to any organ at the time of starting of the treatment (refer case history above). The metastasis from the primary site to other organs lungs, vertebrae, jaws etc. happened within three months from the date of treatment started. It is presumed that the metastasis process might have started after the open biopsy and aggravated after major resection. There was a gap of about one month between date of biopsy and resection (limb salvage). The period between limb salvage surgery (30th Nov) and PET scan (5th Janu) was also about one month. No scan test was performed during the period between biopsy and resection. Only the above PET scan report revealed the metastasis and spread of tumour in other organs. This was a rare case of synchronous metastasis which occurred within a short period of two months from the start of treatment. The earliest metastasis of osteosarcoma cases was also reported by Jeffree et al [5]. It is pertinent here to analyze various factors which possibly influenced such vigorous and synchronous metastasis. As explained above, biopsy may be one of the factors for this synchronous metastasis. In this case, the biopsy method chosen was open biopsy which is considered as more liable for seeding and metastasis [6-10]. Tohme et al [12]. reported that the open biopsy led to poor response to chemotherapy as the former could have served to increase the establishment of new metastasis and accelerated the growth of residual and micrometastastic disease. Trieu et al [4] after analyzing various biopsy reports came with the suggestion, "biopsy in the setting of suspected malignancy is a technically challenging procedure that should only be performed at specialist institutions." In the present case, the open biopsy was performed not by a certified surgical oncologist and not from a specialist institution dealing with surgical oncology. The chief surgeon who performed both surgeries was only an ortho surgical specialist. Kundu [6] questioned the competency of such generalist orthopaedical surgeon performing such specialized operation. Although the needle biopsy is considered as a safer biopsy technique [19,20] open biopsy opted in this case may be due to lack of specialists and specialization in needle biopsy technique or due to ignorance on the advantages of needle biopsy techniques. Vijayakumar et. al [21] in their recent review on impact of preoperative biopsy concluded that, although preoperative biopsy may contaminate biopsy tracts, appropriate surgical planning, and final resection results in no difference in local recurrence rates. In this regard Kundu, [6] suggested various practices to prevent biopsy related tumour cell seeding. More precision needle biopsy techniques are also recently reported [21-23]. Coming to the second issue of side effects of surgical interventions on tumour progression and dissemination, in the present case, the major surgical interventions were the open biopsy surgery and the subsequent limb salvage surgery. Although it was established by a lot of research findings [11-13] the various factors which are responsible for the side effects of surgical interventions on tumour progression and dissemination, not much attention is paid to address this issue now. They [11-13] also suggested various perioperative therapeutic options to minimize their impact. In the present case, this clinical risk was totally ignored, and no attempt was made to minimize the surgical interventions. Only chemotherapy was practiced combating the cancer seeding and its growth. It is now established that the chemo drugs itself could enhance metastasis of primary tumour.

The third important factor to be analyzed is the role of chemotherapy in influencing metastasis of the primary tumour. In the present case the patient was administered neoadjuvant chemotherapy in two cycles after the open biopsy before the limb salvage surgery. It was expected that the primary tumour might shrink before resection. But, in this case the open biopsy area of the leg, instead of shrinking, started painful swelling indicating poor response for chemotherapy drug. This was confirmed in the biopsy test taken after resection. Such poor response was also reported in a similar case by Steinbrecher et al [24]. The chemotherapy drug used in this case was cisplatin which was shown to systematically support tumour growth, resistance to chemotherapy and metastasis in mouse models [25]. Ratajczak

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al. [26] emphasized the need to develop efficient anti-metastatic drugs that will work in combination with, or follow, standard therapies to prevent the possibility of therapy-induced spread of tumour cells. In this connection Fang et al [27]. concluded from their study that, that Snail participates in cisplatin-induced EMT in osteosarcoma cells, and targeting EMT-transcription factors may offer promise for the therapeutics of osteosarcoma. Therapies with nitric oxide, the proteasome inhibitor NPI-0052 targeting NF-κB and Snail were proven to be effective in prostate cancer and B-non-Hodgkin's lymphoma [28].

Although the cisplatin is a recommended and widely used drug for various cancers including osteosarcoma, there are still better drugs for neoadjuvant chemotherapy that are specifically recommended for osteosarcoma. In the study promoted by Huang et al., [29] neoadjuvant chemotherapy consisted of combination of IFO, ADM, and MTX/CIS. This was considered as the most effective neoadjuvant chemotherapy for osteosarcoma with the 3- and 5-year OS rates of 91.3% and 87%, respectively [30]. Regrettably, these latest research findings were not put into practice in the treatment protocol of the patient.

Conclusion

It is concluded that the following interventions for combating the clinical risk factors in the treatment protocol should have been considered for a better survival of the patient concerned and, the same may be considered for any future treatment protocol for osteosarcoma cases to achieve higher rate of success:

i. Treatment from a specialist institution dealing with surgical oncology with the aid of a certified and specialist onco-surgeon.

ii. Safer needle biopsy technique should be the priority that too should be performed by a specialist in that field.

iii. Preventive treatment measures to neutralize the suspected harmful effects of surgical injury induced metastasis.

iv. More effective chemotherapy protocol which is based on outcomes.

v. Various treatment options for neutralizing chemotherapy induced metastasis.

Conflicts of Interest

The Author declares that he has no conflicts of interest.

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The first author dedicates this paper to his beloved late granddaughter whose actual case history has been taken for this present case study.

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