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LETTER TO THE EDITOR

Bone sarcoma during pregnancy: an example of personalized multidisciplinary care

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The presentation of a bone sarcoma during pregnancy is very rare and a challenging situation for all parties involved. Here, we describe a case of a patient who was diagnosed with bone sarcoma during pregnancy and received a tailored multidisciplinary treatment.

A 31-year-old previously healthy Caucasian woman, G2P1, was diagnosed with a high-grade pleomorphic undifferentiated spindle cell sarcoma of the distal femur at 22 weeks of gestation. No metastases were found on a whole-body fluorodeoxyglucose (FDG)-positron emission tomography (PET)-scan combined with low-dose computerized tomography (CT)-scan. Given the clinicopathological characteristics of the tumor, an osteosarcoma protocol was applied. A multidisciplinary team was formed, consisting of a medical oncologist, gynecologist–obstetrician, orthopedic oncologist, pharmacologist and specialized adolescent and young adults (AYA) nurse. After thorough counseling, the patient decided to maintain the pregnancy. The usual neoadjuvant schedule of chemotherapy (cisplatin, doxorubicin and methotrexate) [1] was adjusted in close collaboration with the pharmacologist to minimize the risk of teratogenic effects. Cisplatin and doxorubicin can be used safely, though with caution, from the second trimester of pregnancy [2,3]. Since limited data are available on the administration of the high dose of

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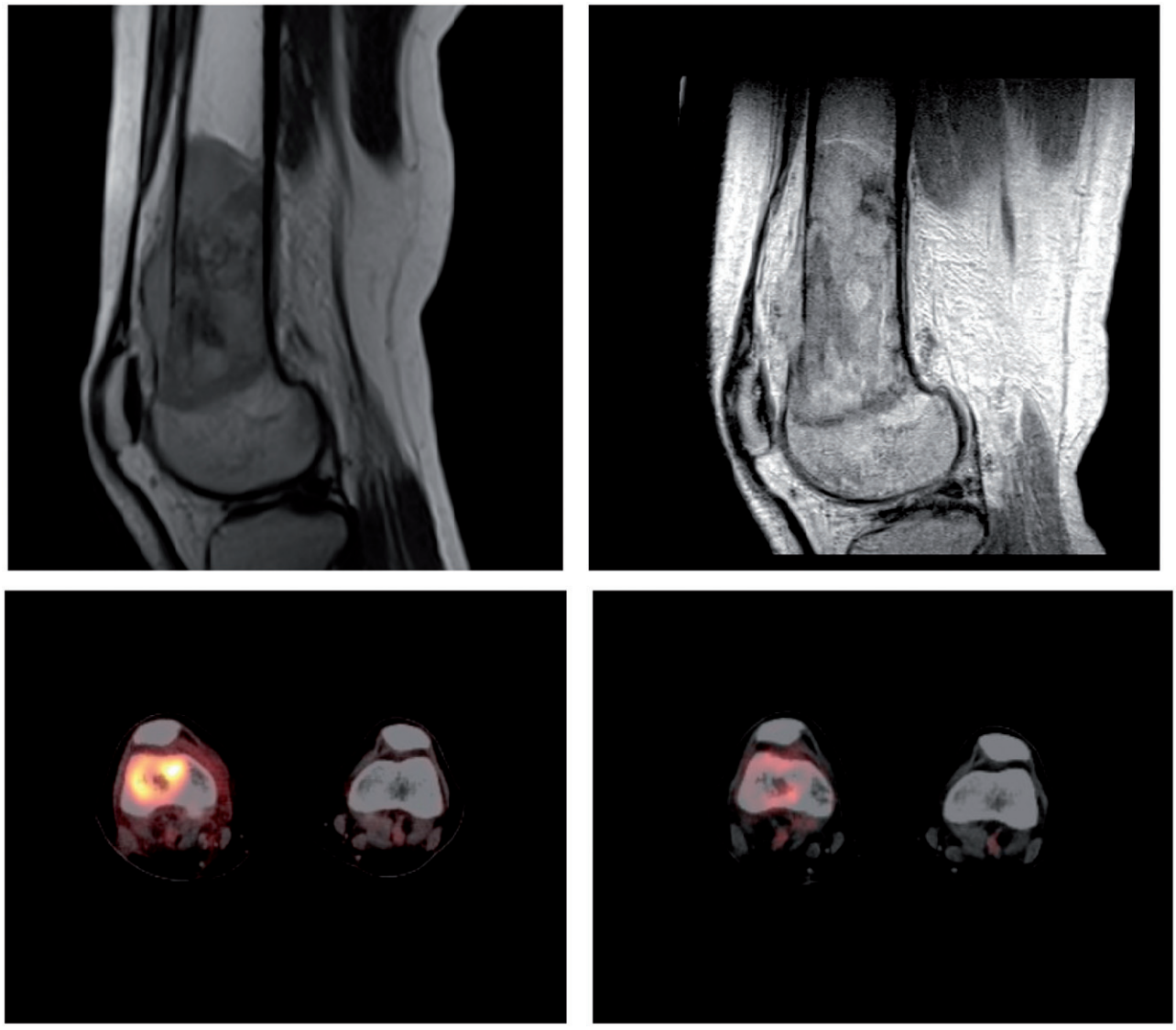

Figure 1. MRI and PET scan showing the tumor before treatment (left) and after two courses of chemotherapy (right).

100 mg/m^2 cisplatin during pregnancy, and to avoid high peak concentrations of cisplatin, the dosage of 100 mg/m^2 was divided over five dosages of 20 mg/m^2 administered over five consecutive days (day 1–5 q 21 d). In order to determine the systemic exposure to free fraction platinum (Pt) in this patient, venous blood samples were obtained during cisplatin infusion. The calculated free platinum area under the concentration time curve ($AUC_{0\text{-}24h}$) after a single dose of cisplatin of 20 mg/m^2 was 0.64 μg*h/ml. The extrapolated AUC_{0-120h} of 100 mg/m^2 given over five consecutive days was thereby 3.19 μg*h/ml. This is considered to be adequate exposure [4]. Because of its highly teratogenic properties, high dose methotrexate was postponed until after delivery.

During chemotherapy, fetal well-being was monitored by the gynecologist. Two courses of chemotherapy resulted in a metabolic but not volumetric response of the tumor (Figure 1). At the pregnancy term of 29 + 5 weeks, we proceeded to limb saving surgery with a mega-prosthesis reconstruction. Fetal monitoring during and after surgery did not show any negative effects for the baby. The diagnosis of a high-grade pleomorphic undifferentiated spindle cell sarcoma was confirmed by the pathologist, with resection margins of at least 2 cm and a therapy effect of 50–60% necrosis, the latter below the preferred percentage of >90%. Because of the necessity of highly teratogenic adjuvant chemotherapy after surgery, prematurely cesarean section was scheduled at 32 + 0 weeks of gestation and a healthy daughter was delivered (weight 1870 g, p50–80, Apgar score 8/9 after 1/5 min). Due to prematurity, but not dysmaturity, the baby was admitted to the Neonatal Care Unit for almost 7 weeks. No adverse effects, especially no hearing impairment, were discovered until the age of 2 years, whereafter she was discharged from further pediatric follow-up.

Eleven days after delivery, adjuvant chemotherapy was started. The treatment protocol was adjusted to comply to the cumulative dosages used in the EURAMOS protocol, which was considered of extra importance since the necrosis percentage was <90% [1]. Furthermore, intensive revalidation was started.

The total treatment plan took 10 months and was challenging for the patient, her family and the multidisciplinary

Table 1. Reported single cases of bone sarcoma during pregnancy.

Study	Age	Term	Tumor	Metastatic disease	Chemotherapy before delivery	Surgery before delivery	Delivery	Outcome maternal	Outcome fetal
Correa 2012	26 yr	33 wks	OS scapula	Y	N	N	CS, 33 wks	†2 d after delivery	Unknown
Schur 2012	27 yr	18 wks	ES pelvis	N	Y VIDE	N	VD, unknown term	NED 11 months FU	†Intra-uterine after 1st course
Quaye 2010	33 yr	33 wks	OS femur	N	N	N	CS, unknown term	NED Unknown FU	Healthy at birth
Kanazawa 2009	38 yr	37 wks	OS lower jaw	N	N	N	CS, 38 wks	NED 3 years FU	Unknown
Nakajima 2004	17 yr	22 wks	ES thigh, extra-skeletal	N	Y DI	N	CS, 32 wks	†7 months after delivery	Delivery: SGA Healthy at 8 months
Merimsky 1999	21 yr	6th month	ES pelvis	N	Y DI	N	CS, 36 wks	NED 24 months FU	Healthy at 24 months
Haerr 1985	21 yr	25 wks	ES pelvis	N	Y T6 protocol without MTX	N	CS, 34 wks	NED 4 years FU	Healthy, low birth weight, mild RDS 2 d. Healthy at 4 years
Lysyj 1963 [13]	21 yr	32 wks	ES pelvis	Y	N	N	CS, 36 wks	†4 months after delivery	Unknown

yr: years; wks: weeks; OS: osteosarcoma; ES: Ewing sarcoma; Y: yes; N: no; MTX: Methotrexate; CS: cesarean section; VD: vaginal delivery; NED: no evidence of disease; FU: follow-up; SGA: small for gestational age; RDS: respiratory distress syndrome; VIDE: vincristin, ifosfamide, doxorubicin, etoposide; DI: doxorubicin, ifosfamide; T6 protocol: Dactinomycin, Cyclophosphamide, Bleomycin, Vincristine and Doxorubicin. †: deceased.

team, and personalized supportive AYA care was offered to them to enable mother and child well-being. By now, we know how important this period has been, since 2 years after completion of treatment, pulmonary and bone metastases were detected for which the patient is currently treated with palliative intent.

Bone sarcomas are extremely rare during pregnancy with only 75 cases reported since 1963. Chemotherapeutic treatment during pregnancy has only been described in four cases of Ewing sarcomas (Table 1) [5–8], despite the fact that a multidisciplinary approach including chemotherapy is standard of care for localized bone sarcomas.

Chemotherapy in pregnancy is safe [9], but needs empirical pharmacological adjustments and careful monitoring. The use of platinum-based chemotherapy during pregnancy is associated with an increased incidence of notification of small for gestational age (OR 3.12, 95% CI 1.45–6.70) [10]. Concerning the long-term effects of exposure to maternal chemotherapy, no significant effects on children's general health, growth, hearing, cardiac function or central nervous system were found [9], thus indicating that chemotherapy can be safely administered after the first trimester.

However, prematurity was significantly associated with impaired cognitive development [9]. The overall frequency of premature birth in patients with cancer during pregnancy is rather high, around 50% [10]. As happened in our case, 88% of premature births were scheduled deliveries based on medical considerations for mother and child [10]. These findings emphasize the importance of carefully considering the timing of delivery.

Despite our appropriate cisplatin AUC_{0-120h} of 3.19 μg*h/ml for the divided doses cisplatin, the percentage of necrosis found in the pathology sample was below the required 90%. In comparison, 50% of the non-pregnant patients treated within the EURAMOS trial had less than 90% necrosis after neoadjuvant doxorubicin, cisplatin and high dose methotrexate. Our patient had the same cumulative methotrexate dose although administered only in the adjuvant setting. Less than 90% necrosis is associated with poor outcome [11].

Surgical treatment of the tumor during pregnancy is safe, but needs consideration regarding timing with respect to both pregnancy term and fetal monitoring, as well as the expected nadir of the chemotherapy. If possible, surgery should be delayed until the second trimester to decrease the risk of teratogenicity and miscarriage due to anesthetics [12]. Effects of the oncologic surgery on the way of delivery of the child in a later phase should also be taken in account, e.g., the newly mega-prosthesis of our patient inhibited vaginal delivery.

With this case we emphasize the importance of a patient-centered approach with an adjusted multidisciplinary team, in the unique setting of a pregnant patient with a curable but unfavorable high grade undifferentiated sarcoma of the bone.

Disclosure statement

No potential conflict of interests was reported by the authors.

Consent

The patient whose case is described in the case report has provided written informed consent for anonymous publication.

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