Delayed diagnosis of an Ewing sarcoma of the knee during pregnancy

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Introduction

The incidence of cancer in pregnancy is approximately 1 in 3000. Ewing sarcoma is a rare tumour, mostly occurring in the bones and soft tissues of children and adolescents (Balamuth and Womer, 2010). It is one of the most lethal of all bone tumours. The incidence of bone tumours (and especially Ewing sarcoma) during pregnancy is extremely low and only a few cases are reported in the literature. We present a case of a metastatic Ewing sarcoma developed during pregnancy, diagnosed after delivery and treated in the postpartum period.

Case report

A 37-year-old woman, gravida 6 para 3 abortion 2, was admitted to our maternity ward at a gestational age of 41 weeks for induction of labour. She had received antenatal care from an obstetrician in a University hospital clinic and from a midwife at home. She presented to the emergency department of the university hospital with an intense pain in the right knee and lower leg since 4 months.. A deep vein thrombosis, one of the most current pregnancy-related problems, was excluded by a negative Doppler examination and the patient was sent home. Over the last two weeks an increased loss of function occurred inducing difficulties with standing up and walking. She was referred again by her midwife to the same emergency ward but no further examinations were performed and she was sent home without a diagnosis. At admission to our maternity ward clinical examination of the painful area revealed a swollen knee, painful and warm at palpation. Because her delivery was imminent, only a blood analysis and an ultrasound of the knee and lower leg were performed. The ultrasound showed the presence of a necrotic/inflammatory collection at the superior part of the tibia with an irregular aspect of the periost and external cortical layer. Underlying bone pathology was therefore suspected, possibly related to osteomyelitis of the superior part of the tibia. Laboratory investigation showed signs of infection (CRP 44, white blood count 11300 cells/μL, neutrophilia 8803 cells/μL). Given the suspicion of osteomyelitis, an antibiotic treatment (Floxacilline) was started. Labour and delivery were uneventful and she gave birth to a healthy boy.

The next day an additional work up was performed. Clinical head-to-toe examination showed the already described findings regarding the right knee and leg, but additionally the astonishing presence of several lumps in both breasts, the largest being a mass of 4 centimetres in the right breast. Blood tests showed normal kidney function tests, slightly elevated hepatic tests, a normal CA 15.3 (14 IU/ml) but an elevated CA 125 (121 IU/ml). Further radiologic examinations, including X-Rays and an MRI of the knee and leg confirmed the presence of a massive destruction of the proximal part of the tibia seen as an infiltrating lesion of the metaphysis of the tibia with signs of resorption (Figure 1). RX thorax revealed the presence of lung metastases in both pulmonary fields. Computer Tomography (CT) of thorax and abdomen confirmed the presence of lung metastases, but showed also peritoneal and multiple bone metastases. Mammography and ultrasound of both breasts not only confirmed the presence of two large lumps, but in addition it showed 12 neoplastic lesions in the right

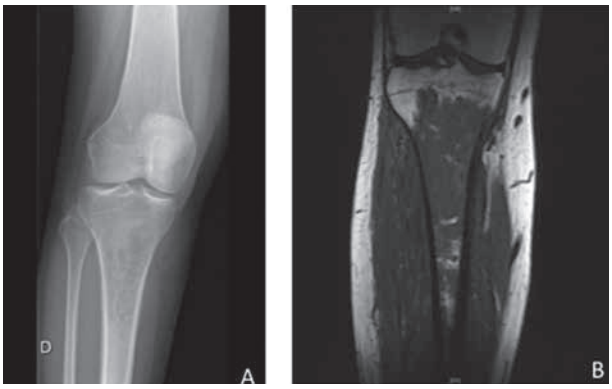

Fig. 1. — A: Periosteal new bone formation showing 'onion-skin' appearance/ B: Axial T1-weighed MRI: infiltrating lesion of the metaphysis of the tibia, expanding to the surrounding tissues.

and 7 neoplastic lesions in the left breast. Finally, a whole bone scan and positron emission tomography (PET) scan confirmed all sites of neoplastic lesions (Figure 2A).

In view of these findings the differential diagnosis of a metastatic breast cancer or metastases of a primary bone tumour was withheld. The microscopic examination of a biopsy of one of the large breast nodules revealed the presence of a small blue round cell tumour, suggesting a primary bone tumour, which was confirmed by immunohistochemistry (CD99 expression) (Figure 3). Additional FISH analysis revealed rearrangement of the EWS gene, and not of the WT1 gene, indicating the diagnosis of Ewing sarcoma (Figure 4). Four days postpartum, chemotherapy was initiated. A 3-week alternating treatment of vincristine/adriamycin/cyclophosphamide (VAC) and etoposide/iphosphamide (IFO-VP16) was given, which was well tolerated apart from slight anaemia and constipation. After one cycle of chemotherapy the patient reported less pain and a reduction of the volume, redness and inflammation around the knee was observed.

After five cycles of chemotherapy, subjective and objective response was excellent and the patient was able to stand up again and walk small distances after a long period of suffering from an intense pain and inability to walk. After the total of nine cycles, the PET-scan showed complete response (Figure 2B).

Since the last studies on Ewing sarcoma showed that additional 5 cycles of chemotherapy increase the durability of the remission, her treatment was extended with 5 extra cycles. Unfortunately, three months after the total of 14 cycles, a solitary brain metastasis was discovered. While writing this case report she just completed one month of stereotactic radiotherapy with complete response.

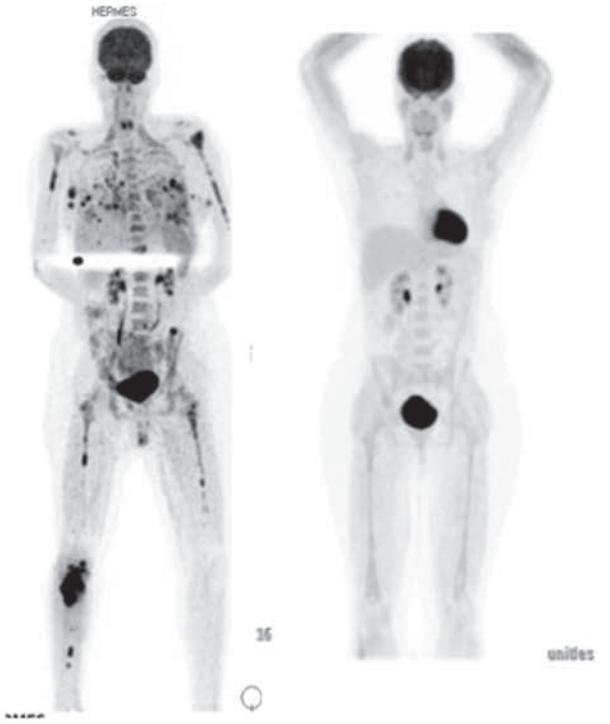

Fig. 2. — PET-scan: A: before chemotherapy: primitive lesion and multiple sites of metastasis/ B: after chemotherapy (9 cycles): complete response.

Discussion

Ewing Sarcoma

Ewing sarcoma is included in the Ewing sarcoma family of tumours (ESFT) including extra skeletal Ewing's sarcoma (EES), Askin tumours of the chest wall and primitive neuroectodermal tumours of bone and soft tissues. It is the second most common primary bone tumour seen in children and adolescents. With a predilection for males, and peak age incidence in the second decade of life, EES is relatively more common in adults of which a quarter presents with metastases at diagnosis (Balamuth and Womer, 2010; El Weshi et al., 2010). Earliest symptoms are pain at the tumour site, increasing in intensity as the tumour grows, followed by the appearance of a palpable mass (Ushigorne et al., 2002; El Weshi et al., 2010). Lesions tend to arise in the diaphysis or metaphyseal-diaphyseal portion of long bones, but also the pelvis and ribs are common locations. On a histological basis Ewing sarcoma refers to a collection of small round cells with pale cytoplasm and small hyperchromatic nuclei (Figure 3). Geographic necrosis and individual degenerating cells are frequently present. Different markers can be expressed; however none of them is specific. Most common is the CD99 expression of

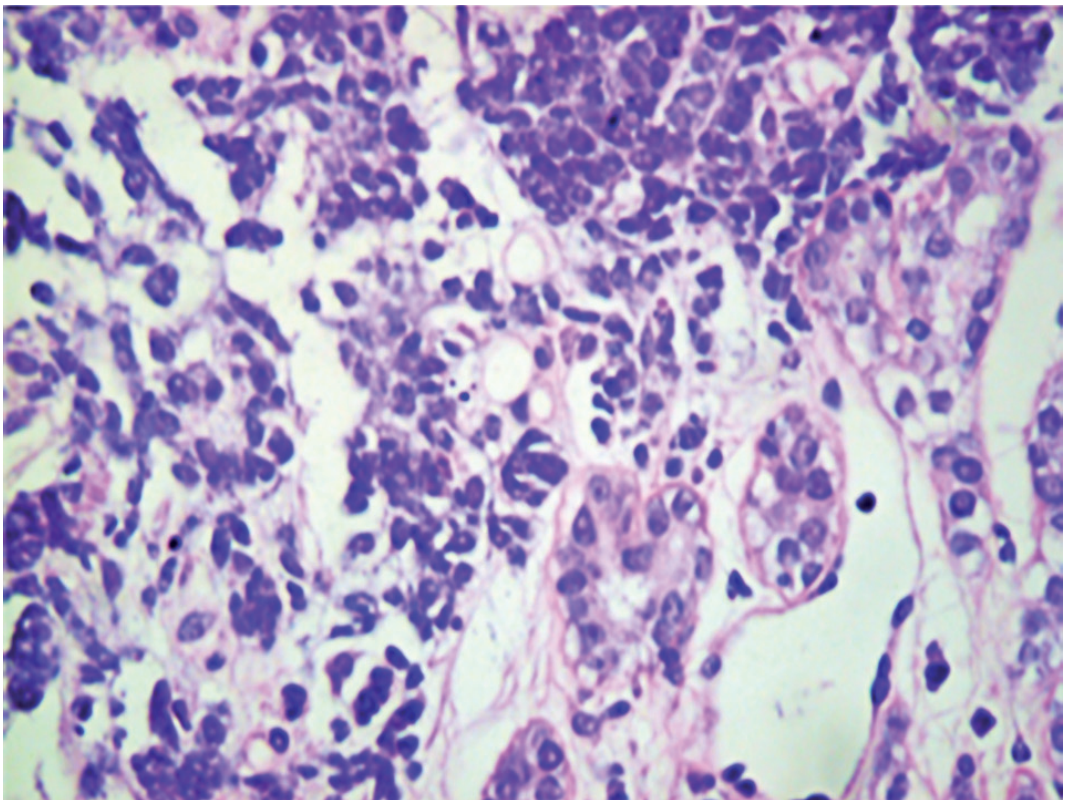

Fig. 3. — Biopsy of a metastatic breast nodule: uniform small round cells with round nuclei.

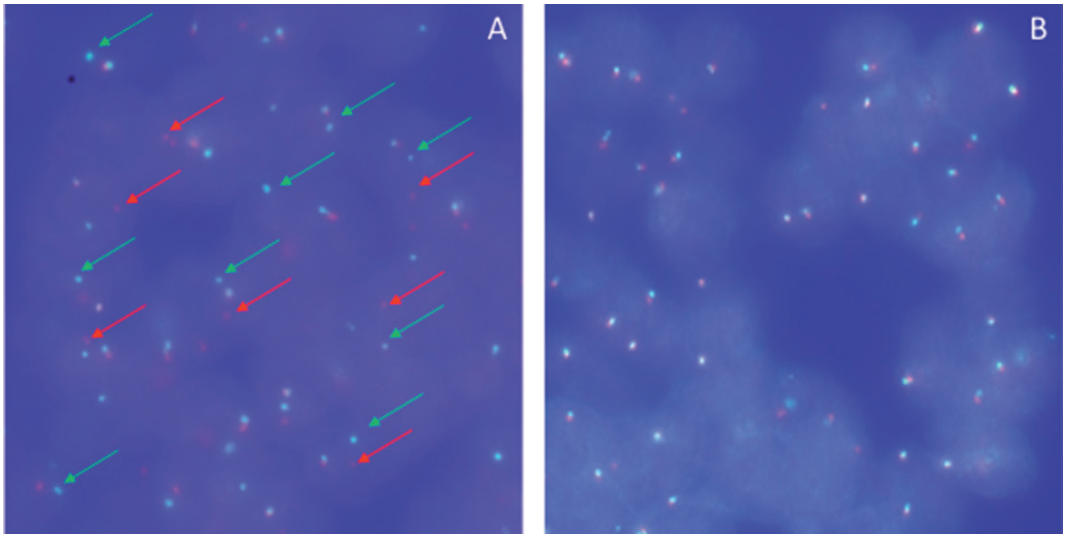

Fig. 4. — Double colour interphase FISH analysis of tumour specimens using break-apart EWS (A) and WT1 (B) DNA probes. The present of split apart green and red hybridization signals (A) indicate EWS rearrangement (marked with arrows). Conversely, WT1 gene was not rearranged as judged by juxtaposed red/green hybridization signals (B).

the membrane, but also vimentin, keratin, and IHC for FLI1 protein can be positive. However it is the characteristic t (11;22) chromosomal translocation and resulting EWS-FLI1 gene fusion that gives a 90% certainty of the diagnosis of Ewing sarcoma. The fusion gene can be detected by fluorescence in-situ hybridisation (FISH) (Figure 4) or by reverse transcriptase PCR (RT-PCR). RT-PCR nowadays can also detect fusion transcripts in peripheral blood or bone marrow, which is a sensitive marker of minimal residual disease. However, they still are exploring the implication of this marker on estimating the risk of recurrence (Balamuth and Womer, 2010; El Weshi et al., 2010).

Table 1. — Summary of case reports on Ewing sarcoma and extra skeletal Ewing's sarcoma diagnosed during pregnancy.

Reference	Diagnosis	Primary tumor site	Metastases at diagnosis	Treatment	Outcome	
					Mother	Infant
Lysyj & Bergquist 1963	primary	case 2: right superior pubic ramus	case 2: right lung base and right parietal bone of the skull	radiotherapy and chemotherapy (5-fluorouracil) after delivery	case 2: died 4 months after delivery	cesarean section, normal newborn
Greenberg et al. 1982	metastases	left tibia	mass of the mid-occipital region, nodule left lower lung, nodules in the placenta	radiotherapy during and after pregnancy, chemotherapy after delivery	died 7 weeks after delivery	vaginal delivery, normal Newborn
Gililland & Weinstein 1983	primary	femur	none	chemotherapy and radiotherapy during and after pregnancy	no evidence of disease 30 months after treatment	cesarean section, normal newborn
Simon et al. 1984	primary	distal femur	none	radiotherapy and chemotherapy after abortion	no evidence of disease 3 months after treatment	elective abortion
Haerr & Pratt 1985	primary	left iliac wing	none	chemotherapy (dactinomycin, cyclophosphamide, bleomycin, vincristine, doxorubicin) during and after pregnancy, radiotherapy and surgery after delivery	no evidence of disease 4 years after the discontinuation of treatment	cesarean section, normal newborn
Loguidice et al. 1986	primary	left ilium	none	chemotherapy (cytoxan, adriamycin) and radiotherapy after delivery	stable situation 17 months after delivery	cesarean section, normal newborn
Dhillon et al. 1993	primary	case 1: left scapula case 3: right humerus	case 1: left parietal area of the skull case 3: none	radiotherapy and chemotherapy (cyclophosphamide, vincristine, doxorubicin) after delivery	case 1: died 4 months after delivery case 3: died 6 months after delivery	Case 1 and 3: vaginal delivery, normal newborn
Merimsky et al. 1999	primary	right sacro-iliac joint	none	chemotherapy (Doxorubicin, ifosfamide, mesna) during and after (doxorubicin, ifosfamide, mesna, etoposide) pregnancy, radiotherapy and surgery after delivery	no evidence of disease 24 months after treatment	cesarean section, normal newborn
Nakajima et al. 2004	Primary	left thigh	none	chemotherapy (doxorubicin, ifosfamide) during pregnancy, radiotherapy after delivery	died 7 months after delivery	cesarean section, small for gestational age
Dubois et al. 2008	metastases	case 1: right ischium case 2: 11th rib	case 1: lung and left frontal lobe and anterior abdominal wall case 2: lung	chemotherapy (vincristine, doxorubicin, cyclophosphamide) and radiotherapy after delivery	case 1: recurrence, no further follow-up case 2: disease-free 13 years after first recurrence	case 1: cesarean section, normal newborn case 2: vaginal delivery, normal newborn
Blight & Puls 1981	primary	retroperitoneal abdominal mass	none	radiotherapy, surgery and chemotherapy (vincristin, cyclophosphamide, doxorubicin) after pregnancy	died 8 months after treatment	vaginal delivery, normal newborn
Gennatas et al. 1987	primary	left thigh	none	chemotherapy (cyclophosphamide, vincristine, adriamycine, DTIC, actinomycin-D) during and after pregnancy	complete remission (duration not known)	cesarean section, normal newborn
Adair et al. 2001	primary	duodenum	none	surgery and chemotherapy after pregnancy	no evidence of disease 10 months after treatment and termination of pregnancy	termination of pregnancy

Cancer and pregnancy

Cancer occurring during pregnancy is a relatively rare problem, with an incidence of approximately 1 diagnosis in 1000 pregnancies. However since women are delaying childbearing and the incidence of cancer in the third and fourth decade is rising, it is expected that the coincidence of cancer and pregnancy will increase. Breast cancer remains the most frequent encountered cancer during pregnancy (46%), followed by hematologic (18%) and dermatologic malignancies (10%) (Van Calsteren et al., 2010). Unlike breast cancer in pregnancy, which has become a hot topic in scientific reports (Amant et al., 2010), other tumours, including sarcoma, are very rare with a lack of large studies.

Literature search

We performed a literature search to find out how many cases of Ewing sarcoma and extra skeletal Ewing's sarcoma during pregnancy have been published (Table I). In total we found 12 case reports of primary Ewing sarcoma diagnosed during pregnancy, and 3 case reports of EES. These 15 cases report mainly on primary diagnosis. Greenberg et al. (1982) and Dubois et al. (2008) report the recurrence of Ewing sarcoma (lung, skull, and placenta), of which the primary diagnosis was made during childhood and adolescence.

Most cases were treated during pregnancy with chemotherapy, radiotherapy, and/or surgery and resulted in a good outcome for both mother and child.

Metastases at diagnosis were only reported in 4 cases, of which 2 were recurrence of the primary tumour diagnosed at young age.

Our case presented with breast metastases which is very rare since only 0,3 to 2,7% of all malignant breast neoplasms are metastases. We only found two case reports of breast metastases one of a primary Ewing sarcoma, and one of an extra skeletal Ewing's sarcoma, but none of these were related to pregnancy.

Because of the scarce presence of primary bone tumours during pregnancy, little is known about the treatment options. Simon et al. (1984) were the first to discuss the treatment with a retrospective study on primary bone tumours during pregnancy. Two cases of Ewing sarcoma were reported, in which an elective abortion was performed because of the lack of experience with chemotherapy.

In all cases there is a tendency of the primary bone tumours to progress more rapidly in pregnancy. Whether this is due to the hormonal environment of increased oestrogens and progesterone or to the increased level of IGF-1 expression on Ewing sarcoma during pregnancy remains to be elucidated. (Olmos et al., 2011).

Conclusion

The diagnosis of primary bone tumours during pregnancy is rare. Our case is the 13th case report and is only the second case reporting on breast metastases. The very low incidence of malignant diseases during pregnancy and the confusion with pregnancy-related symptoms or complaints may cause delay in the diagnosis, as shown in this case. Clinicians should remain vigilant, certainly when complaints of the patient persist.

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