

Case Report

Wrong place at the wrong time: A case of cervical embryonal rhabdomyosarcoma in pregnancy



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ARTICLE INFO

Article history:

Received 9 February 2015

Accepted 12 April 2015

Available online 18 April 2015

Keywords:

Embryonal rhabdomyosarcoma

Botryoid type

Cervical cancer

Cancer in Pregnancy

Neoadjuvant chemotherapy

Pathology

glassy cell, neuroendocrine types, melanoma and lymphoma (Behtash et al., 2003). Embryonal rhabdomyosarcoma (RMS) is extremely rare. We present the second reported case in pregnancy, and describe management of a FIGO 1B1 tumour in pregnancy where a delivery delay was desired. The chemotherapy used pertains to the recommended regime for RMS which is mostly extrapolated from paediatric evidence (Zeisler et al., 1998; Brand et al., 1987). It is the 38th reported case of cervical cancer in pregnancy where neoadjuvant chemotherapy (NACT) has been adopted in order to achieve foetal lung maturity. It is the first case of RMS in pregnancy where NACT has been used.

Case

A 36 year old, with a history of spotting since 13 weeks, presented at 20 weeks of gestation with heavy bleeding and passing “grape-like” tissue. On examination she had a 4 cm exophytic lesion on her cervix which was very friable. Abdominal ultrasound scan was normal and showed no extension of the cervical lesion. Examination under anaesthetic was performed with excision of the mass under spinal anaesthesia. A histological diagnosis of cervical embryonal rhabdomyosarcoma (botryoides) was made (Fig. 2).

With a normal cervical smear history prior six months before the above diagnosis, she had been referred for review of a large cervical polyp. At this time, the lesion appeared clinically and histologically benign (Fig. 1). However, when reviewed again at the time of diagnosis, this was also noted to be embryonal rhabdomyosarcoma. Her obstetric history included two previous caesarean sections (her children now aged four and one), a previous termination of pregnancy for an anencephalic baby, and one first trimester miscarriage.

Staging investigations, MRI and CXR, performed at 24 weeks showed no evidence of metastatic disease. Multi-disciplinary-team review panel recommended, six rounds of chemotherapy starting antenatally with vincristine (1.4 mg m^{-2}), adriamycin (0.75 mg m^{-2}), and cyclophosphamide (1500 mg m^{-2}). During each round, these three medications were administered within 2 days and there were 21 days between each round of chemotherapy. Delivery with caesarean, radical hysterectomy and nodal clearance were performed at 34 weeks. The final

Introduction

Cancer affects approximately 1 in 1000 pregnancies and is expected to become increasingly common. The most frequently diagnosed cancers in pregnancy include breast cancer, cervical cancer, melanoma, lymphoma and leukaemia (Meseci et al., 2014). Cervical cancer makes up approximately 25% of cancers diagnosed in pregnancy (Meseci et al., 2014). Nevertheless, the literature to inform evidence-based practice in this situation remains limited. The management approach in many circumstances is extrapolated from case studies involving non-pregnant women.

There are many factors which may be associated with this alarming trend including; delaying pregnancy into later reproductive years, the potential influence that pregnancy has on tumour growth, and the increased likelihood of diagnosis associated with increased interaction with health services (Meseci et al., 2014).

The most common subtypes of cervical cancer are squamous cell carcinoma and adenocarcinoma, making up approximately 95% of cases (Behtash et al., 2003). More rare varieties include small cell,

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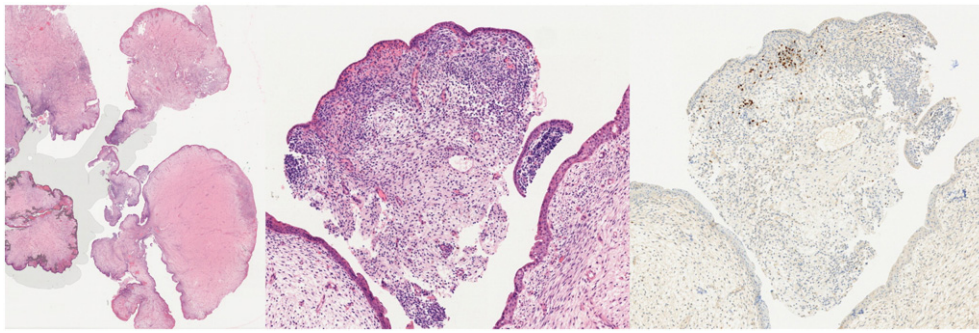


Fig. 1. First cervical polyp, early disease: under low power, high power and myogenin stain.

histology showed no residual tumour. Chemotherapy was subsequently continued.

Antenatally, our patient was seen weekly, with alternating obstetric and gynae-oncology reviews. Fortnightly growth scans were performed and weekly biophysical profiles during the period of antenatal chemotherapy. No significant foetal or maternal complications were encountered antenatally. Post-operatively, after the 4th round of chemotherapy she was admitted with mild neutropenia and a pelvic vault collection that was drained. She also suffered a transient period of moderate short term memory impairment. All of these issues resolved and the patient has remained free from disease to date. Her child had no significant neonatal complications and all developmental milestones have been met to 2 years follow-up.

Discussion

The case represents the second case of embryonal rhabdomyosarcoma (RMS) in pregnancy. In another recently described case, a FIGO stage 1A embryonal RMS was diagnosed at 30 weeks of gestation. Interestingly, there was a delay in diagnosis in this case too as a polyp noted at 6 weeks was initially thought benign (Meseci et al., 2014). In this case the decision was made to delay treatment until foetal lung maturity was achieved at 34 weeks. Then, a caesarean section with radical hysterectomy, pelvic para-aortic lymphadenectomy was performed and adjuvant chemotherapy subsequently commenced.

RMS is extremely rare in absolute numbers and is classically seen in infants or young children. In this age group, it accounts for 4–6% of malignancies (Zeisler et al., 1998; Behtash et al., 2003). The mean age at diagnosis is two years and 90% of cases will occur prior to the age of five (Singhal et al., 1990). A recent case series of all documented cases reports 8 cases in women of reproductive age. RMS is classified into three sub-types: embryonal, alveolar and pleomorphic (Behtash et al., 2003). RMS can arise anywhere, the most common locations being the head and neck (40%), the genitourinary tract (25%) and the extremities (20%) (Dehner et al., 2012). A subtype of the embryonal category is

botryoides (which describes the grossly polypoid “grape like” appearance) first described by Pfannensteil in 1892 (Zeisler et al., 1998). The botryoid subtype is generally found in the vagina during early childhood, the cervix in adolescence and in the uterus during post-menopausal years (Dehner et al., 2012; Zeisler et al., 1998; Behtash et al., 2003; Brand et al., 1987; Daya and Scully, 1988).

Diagnosis can be very complicated. Pathological findings in the early stages of disease may be obscure and a high level of suspicion is required to guide investigations. The microscopic findings in embryonal RMS are relatively consistent irrespective of the organ involved. Including ours, five cases of cervical disease have encountered a delay in diagnosis (Zeisler et al., 1998; Behtash et al., 2003; Garrett et al., 2013). No clear diagnostic features in the early stage of disease have been described in the literature (Garrett et al., 2013). A foci of increased cellularity, indicative of neoplasm, may be the only distinguishing feature and lead to the observed delay in diagnosis (Dehner et al., 2012; Singhal et al., 1990; Zeisler et al., 1998). The differential diagnosis for polypoid spindle cell lesions of the cervix in adult women can be broad and includes endometriosis, cervical or endometrial polyps, adenofibroma, adenocarcinoma, mesodermal polyps, small cell carcinoma and lymphoma. Distinguishing features would include rhabdomyoblasts of varying differentiations (which may be dispersed with loose myxoid stroma) and a cambium layer. Cartilaginous differentiation is also a feature in many cases.

Histopathological features associated with poor prognosis include deep myometrial invasion, lymphatic invasion and focal alveolar pattern (Singhal et al., 1990). Data regarding cytogenetics and heritability of the disease is limited and may comprise a rare cluster of inheritable soft tissue malignancies called the Li-Fraumeni syndrome (Mousavi and Akhavan, 2010). Only one case of embryonal RMS has been cytogenetically analysed (Palazzo et al., 1993). Cervical embryonal RMS has been reported in sisters at age 15 and 17 respectively (Mousavi and Akhavan, 2010). Unfortunately genetic information from these cases is not available. The significance of these findings on their own is limited but it does highlight the importance of having new cases

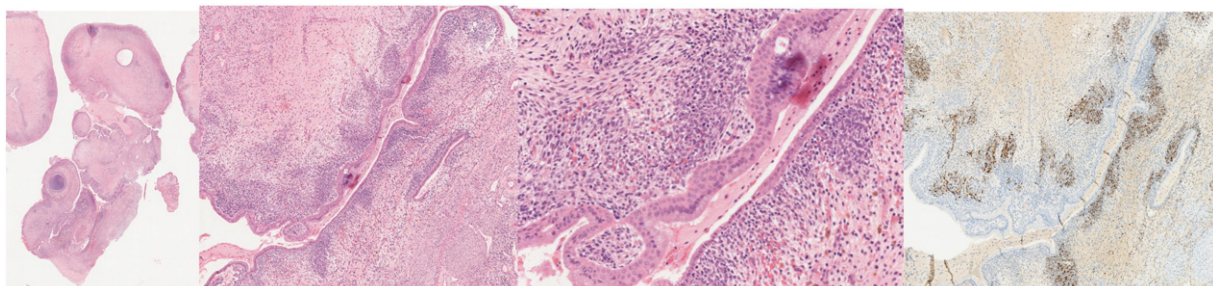


Fig. 2. EUA biopsies — 4 cm exophytic lesion now visible on examination: low, medium and high power, desmin staining.

genetically examined. Furthermore, in the evolving landscape of cancer medicine, individualising treatment based on cytogenetics is increasingly relevant.

Treatment of RMS has evolved considerably over the past several decades. Management of the disease in adults is guided by the paediatric literature and recommendations developed by The Soft Tissue Sarcoma Committee of the Children's Oncology Group (Zeisler et al., 1998). They suggest complete excision for localized disease. If not feasible, an initial diagnostic biopsy followed by NACT, then definitive local therapy is suggested, however, there are no cases of this in the adult cohort. Using combined modality therapy, 70–90% of patients with localized RMS achieve cure. Radiation therapy can enhance local control in patients with residual microscopic or gross disease following surgery.

All reported cases of embryonal RMS in the literature have been managed with primary surgery and subsequent chemotherapy/radiotherapy (Dehner et al., 2012; Singhal et al., 1990; Zeisler et al., 1998; Behtash et al., 2003; Brand et al., 1987; Daya and Scully, 1988; Garrett et al., 2013; Mousavi and Akhavan, 2010). Management in pregnancy is challenging as deliberate delay raises concerns for maternal morbidity, especially when the diagnosis occurs in the first and second trimester. The principles guiding care include the evaluation of tumour size and stage, nodal status, gestation, parental wishes regarding the pregnancy, and histological subtype. This is the first time that NACT has been used and our case suggests good maternal and foetal outcomes. NACT followed by radical hysterectomy has emerged in recent years as an alternative to allow foetal lung maturation in pregnancy (Pettersson et al., 2010). 37 cases of NACT have been described in women with cervical cancer in pregnancy who have FIGO stage >1B1. The advantages of this approach include the opportunity to evaluate the efficacy of the drugs after each cycle, a reduction of the tumour burden to make it operable, and the theoretical treatment of nodal micrometastasis (Pettersson et al., 2010).

Evaluation of the efficacy and safety of NACT in pregnancy is not easy for several reasons but primarily due to the limited number of cases reported in the literature. The cases described to date predominantly involve squamous cell carcinoma and adenocarcinoma (n = 29 78%) (Yousefi et al., 2013). Most cases used single therapy cisplatin with good effect and safety (Yousefi et al., 2013). The chemotherapy regime of paclitaxel, ifosfamide and cisplatin is not recommended due to the nephrotoxic effect of ifosfamide on the foetus (Yousefi et al., 2013). Seven cases used the combination of cisplatin and paclitaxel, and in one case this combination was associated with a severe allergic reaction leading to the onset of pre-term labour (Yousefi et al., 2013). The regime used in our case looked at the use of vincristine, dactinomycin and cyclophosphamide. These drugs have been extensively studied in animals but human data is sparse. Fewer than 10 cases describe the use of each of these medications in pregnancy and this limited data suggests that in the second and third trimesters there is a reduced likelihood of congenital malformations (Kirshon et al., 1988; Nicholson, 1968). Associated problems may include craniofacial dysmorphism, growth restriction, pancytopenia or foetal demise (Kirshon et al., 1988; Nicholson, 1968).

In considering delivery delay, the effect of pregnancy on the tumour and progression of disease is of fundamental importance. To date there is no evidence that pregnancy itself worsens the prognosis for patients

(Pettersson et al., 2010). Many studies show no significant difference in survival between pregnant and non-pregnant women who are matched by age stage and histopathology (Pettersson et al., 2010). There is growing evidence for the use of NACT as an option for women with invasive cervical cancer who do not wish to sacrifice their pregnancy (Yousefi et al., 2013). Therefore, management in a multi-disciplinary team is required with comprehensive counselling regarding the full spectrum of management options. Particular care and monitoring are required when FIGO stage 1B2 or higher occurs to ensure that there is a favourable response to treatment and no signs of progression. Our case is the 38th case where NACT has been used and the first case of embryonal RMS in pregnancy. The results have been most promising.

Conflict of interest statement

The authors declare there is no conflict of interest.

Consent

Informed written consent was obtained from the patient for publication of this report and the accompanying images. A copy of the written consent is available for review of the editor in chief of this journal on request.

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