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Locally advanced cervical cancer complicating pregnancy: A case of competing risks from the Catholic University of the Sacred Heart in Rome

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ABSTRACT

A case of stage IB2 cervical cancer at 27 weeks of pregnancy, treated with neoadjuvant chemotherapy followed by radical Cesarean hysterectomy with full pelvic and infra-mesenteric lymphadenectomy, and adjuvant chemo-radiation is described. While she remains without disease, her baby was diagnosed with acute myelogenous leukemia. We highlight the pre-operative work-up, treatment options, safety, feasibility, and outcomes for the mother and her fetus.

1. Description of case

A 35-year-old nulligravid woman was diagnosed with a poorly differentiated, invasive squamous-cell carcinoma of the cervix at 27 weeks of pregnancy. Two weeks earlier she was admitted to another emergency department for intermittent and persistent vaginal spotting. An ultrasound excluded obstetric conditions such as abruptio placentae and placenta praevia, but pelvic examination showed a large exophytic friable mass involving the cervix. A biopsy confirmed poorly differentiated squamous cell carcinoma of the cervix. A Magnetic Resonance Imaging (MRI) without contrast revealed a 4.0 × 6.2 × 7.0 cm (vol. 90 cm^3) cervical mass involving the entire cervix, with stromal invasion, no parametrial and vaginal infiltration, and no lymphadenopathy (Fig. 1A). Her tumor was classified as International Federation of Gynecology and Obstetrics (FIGO) Stage IB2 with radiographically negative nodes.

A multidisciplinary team including a gynecologic oncologist, obstetrician, radiation oncologist, radiologist, neonatologist, pathologist, and psychologist counseled the patient regarding treatment options, each balancing the potential risks and outcomes for the patient, her cancer and her pregnancy.

The decision to proceed with neoadjuvant chemotherapy (NACT) until fetal maturity was made after thorough discussion with the patient, considering her strong desire to preserve pregnancy, and to reduce risks for fetal survival and health. She underwent 2 cycles of cisplatin (75 mg/m^2) and paclitaxel (135 mg/m^2) at three-week intervals. Chemotherapy was well tolerated. Fetal health was assessed by obstetric US and Doppler velocimetry before and after each cycle.

After two cycles, MRI demonstrated partial response, with a reduction in the tumor size down to 4.0 × 2.2 × 3.4 cm (vol. 16 cm^3) (Fig. 1B). At 35 weeks of pregnancy, three weeks after completing the second cycle of NACT, and after fetal pulmonary induction with steroids, she underwent radical Cesarean hysterectomy (Type C1, according to Querleu and Morrow classification) [1] with bilateral salpingectomy, ovarian transposition, and pelvic and infra-mesenteric lymphadenectomy (Fig. 2). No immediate post-operative complications were noted.

Surgical pathology revealed residual poorly differentiated, invasive squamous-cell carcinoma, 2.5 cm in diameter, infiltrating 1.1 cm of 1.8 cm (61%) the cervical stroma, with extratumoral LVSI, and negative margins (Fig. 3A and B) In detail, microscopic examination revealed the presence of residual neoplastic cells organized in nests and solid sheets, without evidence of keratin pearls formation. Tumor cells displayed a scant eosinophilic cytoplasm with distinct cell borders, and round to oval hyperchromatic nuclei with coarse chromatin. Moreover, the neoplasm showed a brisk mitotic activity of 10/10 HPF and highly positive p16 nuclear staining by immunohistochemistry. Thirty-nine lymph nodes and the placenta were negative for metastases. Adjuvant external beam radiation therapy (4500 cGy in 180 cGy fractions) and concomitant chemosensitization with cisplatin (20 mg/m^2) and 5-FU (100 mg/m^2) was performed.

A healthy male was born, weighing 2450 g, with an Apgar score of 8/9. At 22 months of age, the baby experienced acute myeloid leukemia

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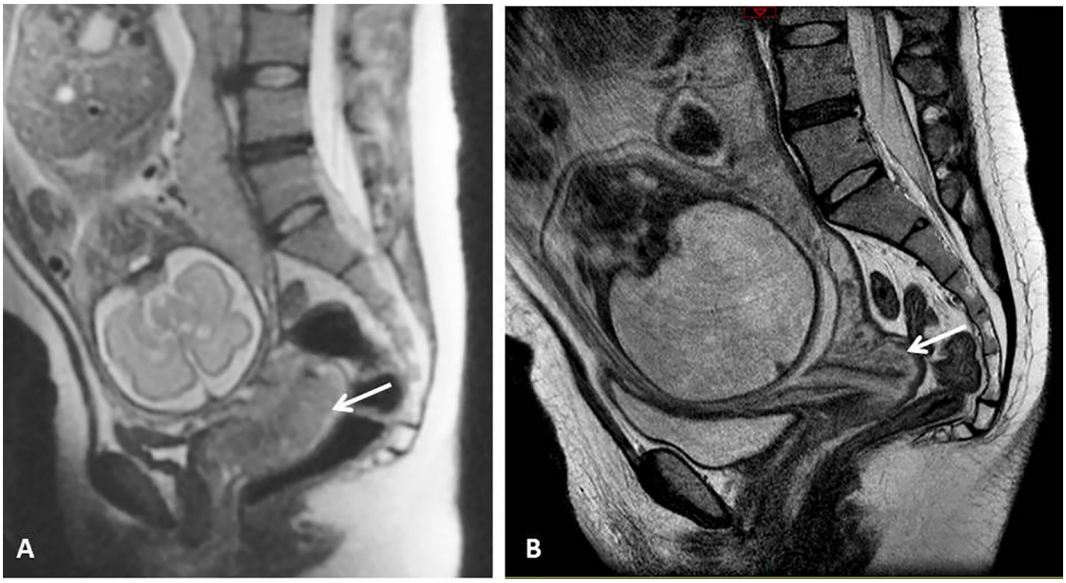

Fig. 1. MRI assessment of cervical tumor diameter. A) 4.0 × 6.2 × 7.0 cm cervical mass (arrow) at diagnosis; B) 4.0 × 2.2 × 3.4 cm cervical mass (arrow) after 2nd NACT cycle.

(AML) ex- FAB (French-American-British)-M7 subtype and received bone marrow transplantation. At the time of this publication, the mother and her child have remained free from disease.

2. Impact of pregnancy on the biology of cervical cancer

In developed societies, cervical cancer is one of the most common malignancies in pregnancy, with an estimated incidence of 0.8 to 1.5 cases per 10,000 births [2–5]. This is also due to a raising number of women delaying their age for pregnancy. Up to 3% of women affected by cervical cancer are pregnant or postpartum at the time of diagnosis [6, 7]. Most patients are diagnosed at an early stage of disease [8, 9]. Although a different behavior of autoimmune diseases during pregnancy has been described, due to a new cooperation among diverse T-cell subtypes in pregnant patients [10], there is no evidence in the literature supporting pregnancy as a trigger event for HPV-related carcinogenesis [11].

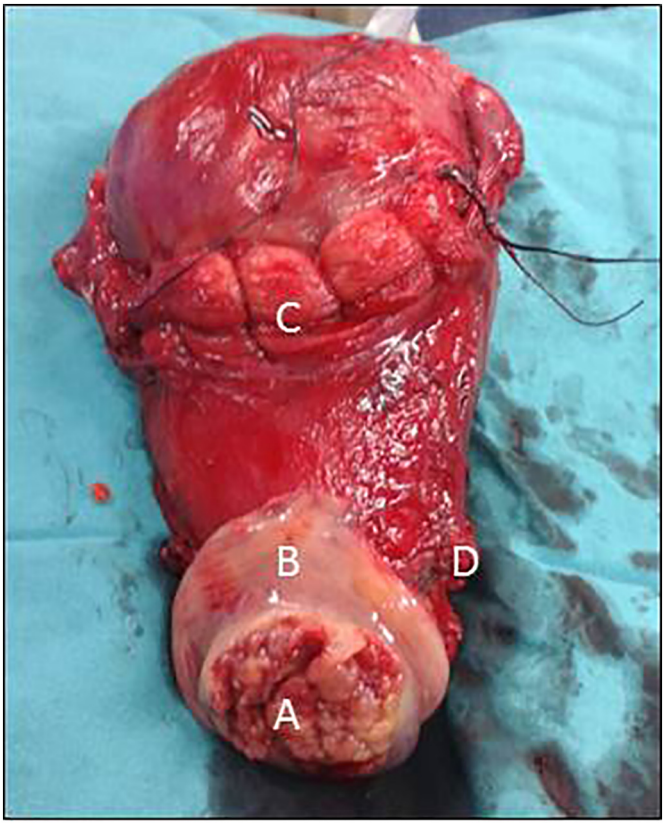

Fig. 2. Radical type C1 Cesarean hysterectomy. A) Residual tumor after NACT; B) vaginal cuff; C) hysterotomy incision; D) proximal paracervix.

As there are no data from large randomized trials that provide guidelines for the treatment of cervical cancer during pregnancy, management takes in account: i) treatment in non-pregnant women; ii) findings from case series and case reports and observational studies of pregnant women; and iii) the unique medical and ethical considerations underlying each individual case. Existing guidelines for preserving pregnancy in cervical cancer pregnant women are shown in Table 1 [12–15]. Due to the low incidence of cervical cancer in pregnancy, centralization in well- equipped facilities is compulsory.

3. Cervical cancer staging, and the implications of pregnancy on these procedures

Staging of cervical cancer during pregnancy should follow the same approach as cases of non-pregnant patients, and includes a bimanual gynecological examination for the assessment of locoregional diffusion of disease. There is no evidence that the large dimensions of the gravid uterus and the hormone-related changes of parametrial tissues can affect such evaluation. Imaging is often utilized to establish radiographic disease distribution, and abdominopelvic imaging is optimally performed using MRI [16, 17] without contrast. Endovaginal ultrasound is an easily available, affordable and low-risk option for evaluating cervical dimensions [18]. Recently, a multi-centric prospective trial has demonstrated a higher accuracy of ultrasound than MRI in detecting parametrial diffusion of disease and tumor diameter [19].The use of (18-FDG) PET-CT scan is contraindicated during pregnancy due to the high fetal uptake of radioactivity [20].

The pathologic assessment of the lymph nodal status before starting any treatment adds important prognostic information. A laparoscopic LND is feasible until the late second trimester, beyond which the dimension of the gravid uterus may preclude the ability to access the pelvic lymph nodes [15]. The role of SLN in early and locally advanced cervical cancer is debated, but promising data have been recently reported. [21, 22] Papadia et al. [23] described two cases of pregnant patients with

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