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Fast and unfavorable course of invasive cancer of the uterine cervix associated with pregnancy despite of a typical treatment. Case report of 35-year-old pregnant multipara

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Summary

Carcinoma of the cervix is the most common malignancy associated with pregnancy. The frequency of cervical cancer is estimated to range from 1/1,200 to 1/10,000 pregnancies. The symptoms of cervical cancer are not specific and can be mistaken as frequent symptoms associated with other pathologies of pregnancy. The diagnostic procedure is similar to the one which should be proposed to unpregnant women. The treatment of cervical cancer depends on gestational age. The final treatment and further prognosis is carried out after delivery. The authors present the case of a 35-year-old woman at 34 weeks of gestation diagnosed with Stage IB cervical cancer. Treatment was delayed until fetal maturity and an elective cesarean section was performed at 36 weeks' gestation, followed by a radical hysterectomy, bilateral salpingo-oophorectomy, and a pelvic lymphadenectomy. Patient underwent adjuvant radiochemotherapy and brachytherapy. Recurrence of neoplastic process was found after one year.

Key words: Cervical cancer; Pregnancy; Total hysterectomy.

Introduction

Carcinoma of the cervix is one the most common malignancy associated with pregnancy. According to the literature its frequency is estimated at approximately 1.2−10.6 cases per 10,000 pregnancies in different populations, while in Poland the frequency of this cancer is estimated from 1/1,370 to 1/2,500 of pregnancies [1, 2], in which 69−83% of invasive carcinomas associated with pregnancy is at Stage I. According to histological classification, 81−87% of them are recognised as squamous cell carcinoma and 7−15% of them are recognised as adenocarcinoma [3]. The mean age of patients suffering from cervical cancer is from 31 to 35 years. The most common symptoms of cervical cancer like spotting, and pain can be disguised by pregnancy, due to the fact that they may be interpreted as the symptoms associated with pregnancy. It is important to be aware of the fact that carcinoma of the cervix is usually asymptomatic, especially in the early stages [2, 4, 5]. For these reasons obtaining of cervical smear in pregnancy should be a routine procedure carried out during the first visit to a gynaecologist. Diagnostic procedures used for detecting cervical cancer in pregnant women are similar to those used for diagnosis of this cancer in unpregnant patients. Main diagnostic procedures include: cervical cytology, colposcopy, and biopsy [6].

Treatment of cervical cancer associated with pregnancy depends on the stage of the cancer and on the gestational age. The choice of the best time for surgery or look and wait management depends not only on the stage of pregnancy but also on the clinical and histopathological characteristics, the depth of invasion, and the grade of tumor's differentiation [2]. This decision should be made jointly by patient and her doctor. Finally the patient's choice of method of treatment must be made based on very accurate information [7]. The expedited treatment is recommended before 20 weeks of gestation, while after this time the treatment can be postponed until the fetus reaches lung maturity [4, 8]. Due to immaturity of the fetal's lungs during the first half of pregnancy, the primary treatment of Stage Ib and IIa of cancer is extended hysterectomy and lymphadenectomy. In this case the delay of the treatment might be a life-threatening situation. The primary treatment of early stages of cervical cancer in advanced pregnancy is a cesarean section accompanied by expedited adjuvant therapy - the Wertheim-Meigs extended hysterectomy combined with radiotherapy.

According to current state of research on cervical carcinoma, planned delay of treatment does not worsen the prognosis. At present it does not seem to be confirmed that pregnancy is causing the progression of the disease [9]. However, the decision about the delay of treatment until the fetus is potentially able to live outside the uterus is usually made by the patient. During this time pregnant woman

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remains under strict observation in order to detect possible progression of the cancer and to institute the treatment after taking into account the level of fetal lung maturity [2].

The prognosis in cervical cancer in pregnant women is not much different from that in unpregnant patients and it mainly depends on the stage of the disease. The overall five-year survival rate for cervical carcinoma in pregnant and unpregnant women is almost the same and the difference is not statistically significant (87.5% of women diagnosed with Stage Ib and 69.9% of women with Stage IIa survive their disease at least five years) [7]. The impact of pregnancy on the progression of cervical cancer is still disputable. It is believed that inhibition of cell-mediated immunity and high level of estrogens may have unfavourable impact on cancer growth. However, the majority of researches indicate that, as far as dysplasia, preinvasive and microinvasive cancer is concerned, the course of the disease among pregnant women is slow and pregnancy does not influence prognosis and overall survival rate in invasive cancer [10]. The treatment depends on the stage of the disease, weeks of gestation, general condition of the pregnant woman, and her attitude towards termination of pregnancy. It should be also conducted interdisciplinary and individually selected [4, 9, 11, 12].

Case Report

A 35-year-old multipara at 36 weeks of gestation in her third pregnancy was admitted to I Department of Obstetrics and Gynaecology of the Medical Centre of Postgraduate Education in Warsaw on 11th of May 2009 in order to finish the pregnancy followed by Wertheim-Meigs radical hysterectomy.

The patient at 27 weeks of gestation was previously admitted on 9th of March 2009 to the Department of Pathology of Pregnancy Municipal Hospital due to gestational diabetes mellitus (GDM G1). In her past obstetric history, she had two pregnancies which were physiological and finished at term. During the stay she was informed about diabetes diet and the rules of glycemic control. In consequence of the fact that she did not have a recent cytology result (last Pap test 2007 – the second group) and abnormalities on speculum examination, she was additionally recommended to have cervical cytology carried out. The patient was discharged from the hospital with saved and live pregnancy. On 20th of March 2009 the cervical cytology was performed. The test revealed high grade squamous intraepithelial lesion (HGSIL) according to the Bethesda System 2001 and a colposcopy was ordered. It was carried out on 14th of April 2009 and confirmed the result of Pap test. The result of the colposcopy biopsy from 15th of April 2009 was carcinoma palnoepitheliale akeratodes infiltrans colli uteri.

Before surgery she was informed about the disease and treatment possibilities and she consented to proposed treatment. On admission, speculum examination revealed as follows: oversized ectocervix, cervical ectropion which was partly covered with normal epithelium, ulceration four cm in diameter limited to the anterior lip, and purulent excretion from endocervical canal. USG examination revealed longitudinal lie, vertex presentation, mean gestational age 37 weeks, estimated fetal weight 3,150 grams, anterior placenta, and normal amount of amniotic fluid.

MRI of lesser pelvis performed on 14th of May 2009 revealed rotated and off-center cervix, diameter: four cm and unclear stroma. In the left lateral side of the cervix and in the anterior lip there were two focuses with a high signal on T2-weight images which sizes were as follows: 7×5×26×9 mm. If all clinical findings were in accordance, it could be invasive malignancy limited to the cervix. There were no signs of invasion into parametrium and vagina. The ovaries were moved by oversized uterus beyond the examined area. Obliteration of the nearest adipose tissue was probably the result of edema and impaired venous circulation due to pregnancy. The lymph nodes enlargement in this area was not observed.

The patient was qualified to cesarean section, hysterectomy with ovaries (on her request), and pelvic lymphadenectomy. On 15th of May 2009 cesarean section was performed using the suprapubic transverse incision. Female infant was delivered 3,520/54, Apgar 10. Afterwards there was performed the Wertheim-Meigs total hysterectomy with ovaries and upper part of the vagina and pelvic lymphadenectomy. A drain in the peritoneal cavity and in the obturator cavity was left. Estimated blood loss: 800–1,000 ml. The perioperative course was uncomplicated and there was no need of transfusion. On 20th of May 2009 the patient and her baby were discharged from the hospital in a state of good health.

Histopathological examination obtained on 27th of May 2009 revealed that macroscopically the cervix was 6.5 cm length and five cm in diameter. An ulceration 4.5 cm in diameter and 0.2 cm in depth could be observed within whole surface of the cervix. In the scope of the posterior lip of the cervix and the external os, there was a white tissue of tumor which constituted up to 90% of the cervical wall and stretched 2.5 cm into cervical canal. The vaginal cuff was 2.5 cm in width without invasion. The dimensions of uterine corpus were 14×13×11 cm, and there were no pathological changes. The fallopian tubes and ovaries were with no pathological changes. Microscopically: carcinoma planoepitheliale microcellulare precipuae akeratodes colli uteri. There was observed an invasion of the tumor into the cervix but not into the uterine isthmus. Right parametrium was almost without pathological changes. The left one: in the scope of one vessel there were emboli consisted of carcinoma cells. The vaginal cuff had normal appearance. The common iliac lymph node on the right side: in three nodes subcapular metastases were observed. The obturator lymph nodes on the left side: in three nodes there was an inflammation. The internal iliac lymph nodes on the right side were without significant changes. The internal iliac lymph nodes on the left side: in one lymph node there could be observed metastasis which filled up to 50% of its volume. There were no pathological changes in the left common iliac lymph nodes, the right obturator lymph nodes, and the right internal iliac lymph nodes.

The patient was referred to the Oncological Centre in Warsaw due to adjuvant therapy. She underwent radiotherapy of the pelvis. The dose of radiation was 4,500 cGy/g/d.fr.180 cGy/g and additionally there was a boost on the left external iliac lymph nodes performed in a dose of 1,500 cGy/g/d.fr.60 cGy/g. The treatment course lasted 33 days. During radiotherapy the patient received five courses of chemotherapy – DDP – 65 mg. From 5th to 19th of October 2009 she underwent brachytherapy HDR located in the top of the vagina in a dose of 22.5 Gy in three fractions up to 0.5 cm depth. The treatment tolerance was good.

In January 2010 CT examination of the abdomen and true pelvis revealed a solid tumor in the abdominal wall with dimensions of 40×60×43 mm. It was situated in the right rectus abdominal muscle on the level of the iliac crest. It was probably a metastasis. The patient was hospitalised from 7th to 12th of February 2010 in I Department of Obstetrics and Gynaecology of the Medical Centre of Postgraduate Education in Warsaw where she underwent a resection of the tumor. Histopathological examination confirmed the presence of carcinoma planoepitheliale's metastases. The pa-

tient was again admitted to the Department because of recurrence of the disease with vomit and severe pain in the area of pubis symphysis. Physical examination on admission revealed a disruption of wound in low pole and presence of purulent excretion was obtained which revealed numerous colonies of Escherichia coli. Sonography showed heterogenous area (sizes 25×20 mm) stretched to the abdominal wall. The abdominal X-rays performed in a sitting position revealed numerous fluid levels in a small and large intestine which indicated obstruction. Surgeon was asked for consultation due to suspicion of a fistula of large intestine and the symptoms of obstruction. The patient was qualified to parental nutrition. Rectal culture was also ordered. It revealed a large growth of Escherichia coli and Enterococcus faecalis. She was prescribed cefuroxime 3×1.5 g iv., metronidazole 3×500 mg iv., diclofenac 100 m 2×1 susp per rectum, nadroparin 0.3 ml sc, and morphine as analgesic.

PET–CT examination (March 24, 2010) which was performed out of hospital showed three small tumors up to 5.5 mm in the right lung, however no accelerated metabolic activity was observed. Apart from that there were no changes in the lungs. The thoracic lymph nodes were not enlarged. A large lesion was observed in the abdominal wall from S2 level to pubic symphysis (71.3 mm). Its largest transverse size (at the level of the top of hip joint) was 62.3×43.5 mm. The lesion revealed accelerated metabolic activity, SUV max 14.5. It did not invade the urinary bladder. There were single implants shown in the peritoneum. The lymph nodes were not enlarged. There were no focal lesions observed in the liver, spleen, and in the kidneys. Probably, as a result of inflammation, the accelerated metabolic activity in the stomach's and duodenum's walls was observed. CT examination (April 7, 2010) revealed an infiltration into peritoneum, omentum, and abdominal wall below a postoperative scar. In the lesion area was observed widened intestinal loop over this lesion with symptoms of subobstruction. The lesion stretched to the urinary bladder which front wall was altered and thickened.

Laboratory tests were collected according to the special procedure for patient suffering from cancer. Morphology (April 15, 2001): leukocytes – 10.2 K/ul, erythrocytes – 3.02 M/uL, hemoglobin – 8.31 g/dl. Other blood tests: urea – 22 mg/dl, creatinine – 0.8 mg/dl, protein – 6.6 G/DL, glucose – 119 mg/dl, albumin 3.2 g/dl, iron 21 ug/dl, CRP – 193 mg/l, ALAT – 22 IU/l, ASPAT – 15 IU/l, and LDH – 51 IU/l.

Because of worsening patient's state of health, the fistula of large intestine and the mechanical obstruction as the result of cancer recurrence, the patient was referred for the surgery. On 22nd of April 2010 she underwent partial resection of small intestine, colon, and resection of malignancy situated in the true pelvis and abdominal wall which was not radical. The ileum was repaired end-to-end and the transverse colon was repaired end-to-side. A proximal colonostomy, appendicectomy, and drainage of the small intestine were performed . During perioperative period two units of PRBCs and two units of FFP were transfused.

The results of laboratory test which was performed after surgery: morphology (April 22, 2010): leukocytes – 16.7 K/ul, erythrocytes – 3.86 M/uL, and hemoglobin – 10.8 g/dl. Other blood tests: urea – 18 mg/dl, creatinine – 0.5 mg/dl, protein – 5.3 g/dL, and albumin – 2.1 g/dl.

The patient was discharged from the hospital and was referred to the Oncological Center in Warsaw due to adjuvant radiotherapy and chemotherapy, however she did notcontinue the therapy. A few months later she was admitted to the I Department of Obstetrics and Gynaecology of the Medical Centre of Postgraduate Education again due to the worsening of her state of health and enterocutaneous fistula. This delay of the proper treatment may have been responsible for this unfavourable course of disease. She was referred to alternative continuance of the chemotherapy in the Oncological Center in Warsaw but she was disqualified from chemotherapy trials because of the worsening state of health and the stage of the cancer. Patient died in September 2010.

Discussion

Extended radical hysterectomy is a treatment of choice in case of Stage Ib cervical carcinoma associated with pregnancy. The aim of this treatment is the total resection of cancer and also the assessment of disease stage. The collected material allows to conduct histopathological examination. The result of this examination is important to make the decision concerning the relevant treatment – radiotherapy or chemotherapy. The extended radical Wertheim-Meigs hysterectomy is an extensive surgery and it is associated with a high risk of complications. The complications' frequency oscillates from several to 70% [9]. The complications are usually as follows: damage of the nervous system structures and ligaments that maintain the normal position of the uterus, damage of parametrium, vesical, and perirectal venous plexuses, as well as venous plexus of the obturator cavity, damage of the ureter, urinary bladder and large arteries and veins during resection of the pelvic, and para-aortic lymph nodes [9]. The frequency of these intraoperative complications is estimated from 0% to 16% [13]. The intraoperative mortality is assessed from 0% to 2% [8]. The frequency of postoperative complications occurring among patients who have undergone Wertheim-Meigs hysterectomy is quite common [9]. The peculiarity of Wertheim-Meigs hysterectomy and its range cause higher and additional risk of complication among pregnant women who are treated because of cervical cancer. At the same time, adjuvant therapy may also caused some complication, for example the intestinal injury which concerned in the present patient. These can be divided into early and late radiation complications. Early severe complications can be observed in 1.1% of patients whereas early moderate radiation complications occur in 41% of patients. Moreover they are more frequent among patient treated with surgery and adjuvant radiotherapy than in patients treated with radiotherapy alone. The second risk factor is the time between surgery and radiotherapy, especially when it is less than four weeks [14]. The pregnancy is a state which constitutes additional risk of complications [7]. The lesser pelvis of pregnant women is highly vascularised and the performing of such extensive surgery followed by cesarean section is associated with even higher risk for patient than mentioned above. The high level of perimetrium's and perivaginal's vascularisation among pregnant women is connected with higher risk of intraoperative and postoperative complications in connection with unpregnant women. During preparation for the surgery it is very important to perform MRI examination which allow to assess the stage of the disease. In spite of high risk of complications, extended radical hysterectomy is the only known surgery

which may save both mother's and child's life. The prognosis depends on the stage of the disease, patient's age, state of health, socio-economic status, as well as the level of medical knowledge and technical opportunities of the hospital [2, 4, 8, 15]. Identification of the full list of predictor factors, doctors' appropriate knowledge, and experience allow choosing the best treatment procedure. The decision should always be taken after consultation with the patient. She must be informed about advantages and disadvantages of the proposed treatment and possible consequences for the infant because of preterm delivery. During pregnancy, woman is more often examined than ever before. The proper diagnosis before pregnancy is a very important prognostic factor. The prognosis is better if the diagnosis is known at early pregnancy because of the possibility for immediate treatment. The diagnosis in advanced pregnancy is usually associated with higher stage of the disease and higher risk of recurrence and complication which may lead to patient's death [15].

According to Polish Gynecological Society Guidelines, all women should begin cervical cancer screening three years after they begin having vaginal intercourse, but no later than when they are 25-years-old. Screening should be conducted every year with a regular Pap test. Women who have normal Pap test results and do not have any additional risk factors of cervical cancer may get screened every three years. Women older than 30 who have had three normal Pap test results in a row or women after total hysterectomy may also get screened every three years. Every year examination is required for women who have HIV infection, oncogenic HPV types infection, and those who are taking immunosuppressive drugs [16]. Moreover Polish Gynecological Society recommends performing Pap test before conception if the last Pap test has been performed over six months earlier and/or during first antenatal appointment with a gynecologist [17]. These guidelines had been followed by the present team, but it did not protect the patient before the development of invasive cancer. In different countries, cervical cancer screening programs are similar to this performed in Poland. Usually, it is recommended to begin cervical cancer screening at 20-30 years and extending to 60-65 years, at a three- or five-year intervals [18]. The duration of progression from a precancerous phase to cervical cancer is quite long, and it is estimated to occur at ten to 12 years [19]. The progression of disease in the present authors' patients is surprisingly fast and it may dispute their current knowledge regarding tumor biology during pregnancy, especially in the third trimester. Unfortunately, the management guidelines for these patients remain unclear. Some authors have recommended that maximum delay of treatment may be 12 weeks for Stage Ib1 tumors and six weeks for Stage Ib2 tumors [20]. According to French recommendations for management of pregnant patients with invasive cancer, in case of Stage Ib2 cancer diagnosed after 22 weeks of gestation, the acceptable delay in treatment should be less then six to eight weeks [21]. However, in other studies the delay of definitive treatment of Stage Ib of disease only for four and six weeks led to patients' death [22].

The present patient was admitted to the hospital because of gestational diabetes mellitus. There were abnormalities observed on speculum examination. It is controversial why colposcopy or at least a cervical cytology during her first hospitalization was not carried out. These tests could accelerate the diagnosis of cancer. In this case the time between the first hospitalization and the histopathological examination's result was about 40 days. The result of her previous Pap test was the second group. Usually the progression to cancer is slower than two years. The reason of this unexpected fast progression might be false negative result of cervical cytology. It should be remembered that the sensitivity of cervical cytology is only about 70-80%. The second reason of this situation might be the fact that pregnancy is a state which helps the development of cervical cancer via two mechanisms. First is the fact that higher vascularisation of lesser pelvis is probably responsible for faster progression of the disease and metastases. Moreover changes in the activity of immune system may weaken the immune response. It may be considered whether the pregnancy should be terminated after 34 weeks of gestation after the previous steroid therapy. Many researchers claim that after this time infant's life expectancy is similar to that which occurs among full-term infants [21, 23-26]. It should be also obligatory to perform a Pap test in the first trimester of pregnancy regardless of last cytology result. If there are any doubts, a colposcopy should be performed.

As long as we do not have clear recommendations about the management of cervical cancer during pregnancy, this tumor will still remain a clinical challenge. Apart from this, treatment of these women in specialistic hospitals and hastening of diagnostic procedures, particularly during third trimester, seems to be reasonable. Verification of screening scheme during pregnancy should be also considered, especially in a group with additional risk of cancer development.

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