VIA MEDICA

CASE REPORT

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Multiple primary malignancies and cancer during pregnancy — a case of two rare consecutive conditions

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Oncology in Clinical Practice
DOI: 10.5603/ocp.103724

ISSN 2450–1654
e-ISSN 2450–6478

ABSTRACT

Cancer during pregnancy is a rare condition involving neoplasm diagnosed during pregnancy or within a year after labor. Cancer symptoms may be masked by pregnancy symptoms, which might delay diagnosis and proper treatment. Another rare phenomenon is the occurrence of multiple primary malignancies. This is defined as the appearance of two or more unrelated neoplasms in one individual, which can be located in the same or various organs. The risk is increased due to advances in cancer treatment, resulting in a growing population of cancer survivors. Since the co-occurrence of both conditions has not been previously described, we present a rare case report of a forty-year-old female patient who received these two diagnoses. The patient with a colorectal cancer family history in her third pregnancy suffered from painful lesions located in the anal area diagnosed as hemorrhoids. In the next pregnancy, the symptoms were not resolved, and the in-depth diagnosis revealed colorectal cancer. The treatment included chemotherapy during pregnancy and radical surgery involving rectum amputation in the post-partum period. Postoperative magnetic resonance imaging (MRI) revealed a fluid lesion located near the posterior vaginal wall. The cyst's enlargement was observed in the following months, raising oncological concerns. The patient underwent a laparotomy, during which an intraoperative histopathological examination found mucinous endometrioid adenocarcinoma. Optimal cytoreduction was performed, and the patient received post-surgery chemotherapy. The tests performed did not indicate the genetic background of either neoplasm. This case suggests the need for increased oncological vigilance in cancer survivors, as well as pregnant patients.

Keywords: cancer during pregnancy, multiple primary malignancies, colorectal cancer
Oncol Clin Pract

Introduction

Cancer during pregnancy is a neoplasm diagnosed in pregnancy or up to a year after labor. It affects approximately 1.5% of pregnant women, but due to diagnostic difficulties, its prevalence is believed to be underestimated [1, 2]. Cancer during pregnancy is a diagnostic challenge due to masking disease symptoms by the developing pregnancy. This includes constipation, flatulence, or microcytic anemia resulting from iron deficiency, which is common during pregnancy. Typical nausea and vomiting, as well as associated weight loss, which are common pregnancy symptoms, may mask cachexia from expansive tumor development. Also, physiological hyperplasia in the mammary glands affected by hormonal changes and skin hyperpigmentation resulting from increased melanotropin levels may hide developing neoplastic lesions in the breasts and skin. Hence, the cancer diagnosis is often delayed [3, 4]. Among the most common cancers complicating

Received: 25.11.2024 Accepted: 29.11.2024 Early publication: 14.01.2025

pregnancy, breast cancer, thyroid cancer, melanoma, lymphomas, and cervical cancer have been listed [5, 6].

Diagnosing one malignant lesion does not exclude future recurrences or the occurrence of another cancer type. Primary multiple neoplasms are defined as the appearance of two or more unrelated neoplasms in one individual, which can be located in the same or various organs [7]. Based on the period between diagnoses, they are divided into synchronous, when the period between diagnoses is shorter than 6 months, and metachronous, when the period between diagnoses is longer than 6 months [8]. To be classified as multiple primary malignancies (MPMs), the following diagnostic criteria must be met: every lesion has to be verified as malignant by histopathological examination, and their pathological morphology has to be diagnosed as different, metastasis and recurrence must be excluded, and if the lesions are within the same organ, 2 cm of normal tissue needs to be preserved between them [8, 9]. Patients with prime tumors have an increased risk of developing subsequent ones compared to the general population, and even every 1/5 of them develop another neoplasm [10–12].

Considering the data on cancer during pregnancy and primary multiple neoplasms, the occurrence of both conditions seems extremely rare. Recent literature did not find any association between cancer during pregnancy and increased risk of another malignancy development [13]. Thus, we present a case report describing the patient burdened with both these diagnoses.

Case presentation

A forty-year-old female patient had a family history of colorectal cancer (CRC). The patient's grandfather and sister were diagnosed with cancer, and the woman died at the age of thirty-four. Our patient did not suffer from any chronic diseases and had a history of two physiological pregnancies that ended with natural births. In the third pregnancy, the patient reported the presence of painful lesions around the anus. She consulted this ailment with the gynecologist, and hemorrhoids were suspected. During the natural birth, a four-centimeter lump slipped off the anus. The patient consulted with a surgeon, who recommended an ambulatory proctologist consultation after discharge.

During the appointment, the woman was examined per rectum, and a hemorrhoid diagnosis was made. Nevertheless, due to the persistent symptoms and no effects of conservative treatment, a colonoscopy was performed one year later. The examination revealed the presence of a polyp, which was removed and subsequently submitted for histopathological examination. The result was a tubular adenoma with low-grade dysplasia. Four months after that diagnosis, the patient became pregnant for the fourth time. At the turn of the first and the second trimester, the patient had enlarged right inguinal lymph nodes. Ultrasound scans showed a suspicious character of the lymph nodes (Fig. 1A). A fine needle biopsy showed the presence of scattered squamous epithelial cells with atypia and single structures correlated with keratin pearls. In oligobiopsy, metastatic keratinizing squamous cell carcinoma was identified. Thus, the patient was qualified for a colonoscopy, which revealed ulceration of the posterior wall of the lower rectum (Fig. 1B, C). Histopathological examination indicated the diagnosis of low-grade keratinizing squamous cell carcinoma G3. The patient underwent three cycles of chemotherapy with doxorubicin and cyclophosphamide, which were administered in the 23rd, 26th, and 29th weeks of pregnancy. A planned cesarean section was performed in the 34th week of pregnancy, and the general condition of the newborn was good. The treatment with radiotherapy and chemotherapy consisting of mitomycin and 5-fluorouracil (5-Fu) was continuous in the post-partum period.

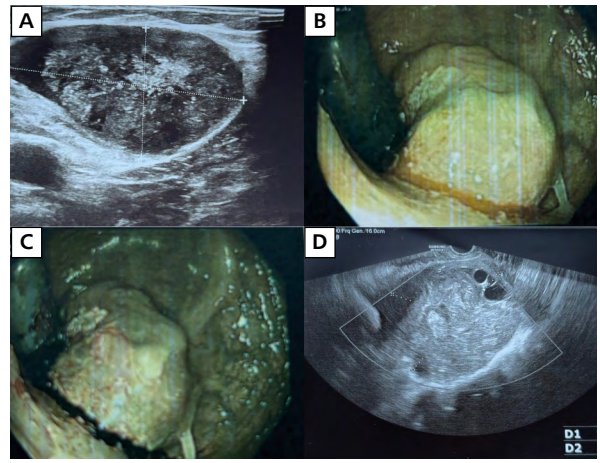

Figure 1. A. Ultrasound image of the atypical inguinal lymph node; **B, C.** Colorectal cancer found in colonoscopy examination; **D.** Ultrasound image of the ovarian tumor

In the subsequent months, the patient underwent follow-up imaging tests. Magnetic resonance imaging (MRI) showed an annular protrusion of the lower rectal wall. In addition, two enlarged lymph nodes in the mesorectum and inguinal nodes were found. Positron emission tomography (PET) demonstrated increased metabolic activity in these nodes and the rectum. Then, 3 months later, the patient was qualified for surgery, during which the rectum was amputated, the right inguinal lymph nodes were removed, and a colostomy was performed. Final histopathology confirmed low-grade squamous cell carcinoma.

On MRI scans from the postoperative period, in addition to postoperative lesions in the projection of the removed rectum, a thin-walled fluid cyst measuring 31 by 16 mm was described. The lower edge of the fluid

Table 1. Results of assessing the panel of genes with the next-generation sequencing (NGS) method

Assessed genes	Collected material	Results
AIP, AKT1, ALK, APC, ARAF, ATM, ATR, AXIN2, BAP1, BARD1, BLM, BMPR1A, BRAF, BRCA1, BRCA2, BRIP1, BUB1B, CASR, CDC73, CDH1, CDK4, CDKN1B, CDKN2A, CFTR, CHEK1, CHEK2, CTNNB1, DICER1, EGFR, ENG, EPCAM, ERBB3, ERCC2, ERCC3, ERCC4, ERCC5, EXO1, EXT1, EXT2, FAN1, FAM175A, FANCA, FANCB, FANCC, FANCD2, FANCI, FANCL, FANCM, FH, FLCN, FOXE1, GALNT12, GATA2, GDNF, GNA11, GNAQ, GNAS, GREM1, HNF1A, HNF1B, HOXB13, HRAS, H3F3A, KIF1B, KIT, KRAS, LZTR1, MAX, MC1R, MEN1, MET, MITF, MLH1, MLH3, MRE11A, MSH2, MSH3, MSH6, MUTYH, NBN, NF1, NF2, NOD2, NRAS, NTHL1, NTRK1, PALB2, PDGFRA, PIK3CA, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PRKAR1A, PRSS1, PTCH1, PTCH2, PTEN, RAD50, RAD51, RAD51C, RAD51D, RB1, RECQL4, RET, SF3B1, SLX4, SMAD4, SMARCA4, SMARCB1, SMARCE1, SPINK1, STK11, SUFU, TGFBR2, TERT, TMEM127, TP53, TSC1, TSC2, WRN, WT1, VHL, XPA, XPC, XRCC1, XRCC2, XRCC3	Blood serum	Known pathogenic or potentially pathogenic variants of mutations have not been detected

lesion reached the posterior vaginal wall. In the following months, the enlargement of the cyst was observed from 58 to 102 mm in diameter, which raised oncological concerns. The patient underwent diagnostic laparoscopy with drainage of the cyst in another treatment center. More than six months later, in an ultrasound examination, the presence of a cystic-solid tumor associated with the uterus was observed (Fig. 1D). The observation was confirmed by a computed tomography (CT) study. Then, the patient was qualified for an oligobiopsy of this lesion.

The woman underwent a laparotomy, which revealed a tumor involving the uterus and adnexa on both sides. The lesion, measured approximately 15 cm, was immovably attached to the sacrum. On the peritoneal surface anterior to the uterus, gelatinous secretion was presented. An intraoperative histopathological examination was performed, which indicated the presence of a mucinous tumor with small foci of calcification. Consequently, the uterus with tumor and uterine appendages and, subsequently, the greater omentum and appendix were removed. The histopathological examination showed partially mucinous endometrioid adenocarcinoma with the appearance of microcalcifications. Due to unresectable lesions, a radical procedure could not be performed. The patient was qualified for six cycles of chemotherapy consisting of paclitaxel and carboplatin. The patient also underwent genetic tests for known mutations predisposing to the co-occurrence of both cancers. However, no significant results were revealed (Tab. 1).

Discussion

Colorectal cancer during pregnancy is a rare condition, representing less than 1% of pregnancy-associated cancers [14, 15]. Due to the increased age of pregnant women and the younger age of CRC occurrence, the number of CRCs during pregnancy is expected to rise [16, 17]. A significant diagnostic challenge is the non-specificity of the manifestations, which often resemble typical pregnancy symptoms. Symptoms such as vomiting, weight loss, anemia, fatigue, anorectal bleeding, and perinatal contractions can easily be misdiagnosed as signs of typical conditions associated with pregnancy [15, 18].

The process of diagnosing cancer in pregnant patients poses many problems due to the limited possibility of using standard diagnostic tools. One of the diagnostic methods for CRC diagnosis, a colonoscopy, can be performed on pregnant patients [16, 19]. In diagnosing pregnant patients, imaging methods involving ionizing radiation, such as CT, PET, radiography, and fluoroscopy, are not the first-line methods, and should be carefully used [20].

It is possible to perform CT on pregnant patients. However, indications for the examination should be carefully determined [21]. Performing CT on areas relatively distant from the abdominal cavity, such as the head, neck, or limbs, is relatively safe. It is believed that the indirect exposure of the fetus due to the dispersion of radiation in the mother's body is negligible [22]. However, in the case of direct radiation exposure to the abdominal or pelvic area, where the fetus is located, a significant risk occurs. In such cases, the potential benefits and possible risks of the examination should be considered. However, when there are life-saving indications for the mother, CT should be performed [23]. Although the doses of radiation in a single CT examination are relatively safe for the fetus (they do not exceed 50 mGy), their possible accumulation in the diagnostic process should be considered. For this reason, treatment should be conducted following the as low as reasonably achievable (ALARA) principle, using a radiation dose as low as reasonably feasible to avoid the danger of its accumulation [24].

Positron emission tomography-CT, another method involving ionizing radiation, can also be used when there are indications. Nevertheless, while 18F fluorodeoxyglucose (FDG) and technetium 99 m can be offered to pregnant patients, iodine-131 should not be used [22, 25].

Ultrasonography (US) and MRI due to the lack of ionizing radiation are the first-choice imaging methods to assess tumor size and lymph node involvement in pregnant patients suffering from cancer [25]. Ultrasound allows us not only to assess the well-being of the mother and fetus but also to evaluate the development of cancer in certain organs, including the thyroid, breast, or lymph nodes [22, 26]. Magnetic resonance imaging is preferred when ultrasound results may be confusing and significantly affect the diagnosis or choice of treatment. Moreover, this method enables assessing a greater scope of organs, including those located deeper in the pelvic or abdominal cavity [22, 27].

Similar to diagnosis, treatment should also consider the potential benefits and risks for the mother and fetus. Therapeutic management depends on the confirmed gestational age due to the dependence of possible complications on the degree of fetus maturity. There are also significant differences in drug pharmacokinetics observed in pregnant patients, e.g., related to changes in the volume of distribution, drug clearance, and metabolite activity [28–30].

Possible therapeutic interventions depend on CRC progression and pregnancy advancement. One therapeutic approach includes immediate termination of the pregnancy or chemotherapy treatment during pregnancy. The third possibility involves systemic chemotherapy after childbirth. Nevertheless, there are no dedicated standards for CRC treatment in pregnancy. When circumstances permit, postpartum chemotherapy is preferred. However, recent literature reports that unlike in the I trimester, chemotherapy in the II and III trimesters of pregnancy has no serious adverse effects and is relatively safe for mother and child [31, 32].

Standard chemotherapy typically contains 5-Fu and oxaliplatin. The effectiveness of FOLFOX (folinic acid, 5-Fu, oxaliplatin) and FOLFIRI (folinic acid, 5-Fu, irinotecan) in pregnant patients has been reported. During the II and III trimesters in metastatic and locally advanced CRC, neoadjuvant FOLFOXIRI (folinic acid, 5-Fu, oxaliplatin, irinotecan) should be considered due to better outcomes compared to standard preoperative chemoradiotherapy [33]. Chemotherapy should be continued up to the due date to prevent the elevated risk of complications related to treatment, such as bleeding or bone marrow suppression [34].

Advances in cancer treatment and increased early-stage disease detection have resulted in a bigger population of cancer survivors who are at risk of MPMs [12, 35].

Certain anticancer therapies, such as chemotherapy or radiotherapy, trigger carcinogenesis [12]. Radiotherapy destroys cell DNA and leads to the formation of primary cloned cells with genetic changes [8].

Another treatment that may induce secondary primary neoplasms (SPNs) is chemotherapy. It is well-known for its leukemogenic potential; however, especially alkylating agents have also been reported to contribute to the development of non-hematologic SPNs [12].

The particular molecular mechanism that causes multiple carcinogenesis remains undetermined [36]. Genetic factors such as single nucleotide polymorphism, microsatellite instability, chromosomal instability, and epigenetic changes contribute to the development of multiple primary tumors [37].

Current literature indicates an increased risk of ovarian cancer in individuals previously diagnosed with CRC. Researchers hypothesize that such statistics are related to genetic-based Lynch syndrome involving co-occurrence of both malignancies [38, 39]. However, the exact reasons for the spontaneous occurrence of CRC and ovarian cancer have not been described so far.

Conclusions

Pregnancy does not exempt clinicians from increased oncological vigilance, and symptoms that may indicate cancer should not be ignored, even if they are typical of pregnancy. Similarly, cancer survivors require oncological vigilance to detect possible recurrences or new malignancies. Importantly, it should be noted that co-occurring cancers may be spontaneous rather than caused by wide-known mutations.

Article Information and Declarations

Ethics statement

Written informed consent was obtained from the patient.

Author contributions

I.D.: conception and design, provision of study materials; data analysis and interpretation, manuscript writing, final approval of the manuscript; K.F.: conception and design; data analysis and interpretation, manuscript writing; N.O., M.J., P.M.: data analysis and interpretation, data analysis and interpretation, manuscript writing; E.W.: data analysis and interpretation, manuscript editing, final approval of the manuscript; G.P.: conception and design, provision of study materials, administrative support, final approval of the manuscript.

Funding

None.

Acknowledgments

None.

Conflict of interest

The authors declare no conflict of interest.

Supplementary material

None.

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