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Case Report
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Ectopic Pregnancy Occurring Under Colorectal Cancer Treatment: A Case Report

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Abstract

Introduction: Pregnancy in cancer patient is rare and tends to produce unspecific symptoms until advanced stage. Therefore, common manifestations of ectopic pregnancy must be properly evaluated to avoid delayed diagnosis.

Case: A 31 year-old woman, carrying a copper Intra Uterine Device (IUD), presented with abdominal pain and increase in pregnancy markers while she was receiving treatment for colorectal adenocarcinoma by oral chemotherapy accordingly to the stage of disease. After a positive pelvic ultrasound, Magnetic Resonance Imaging (MRI) confirmed a right adnexal mass next to the right ovary as well as abundant ascites. These findings were related to an ectopic pregnancy. Two intramuscular and one *in situ* methotrexate injections were performed because of the persistence of the pelvic mass and the stagnation of Beta-HCG level.

Discussion: Pregnancy during treatment of colorectal carcinoma is a rare event and its diagnosis is often delayed because symptoms are unspecific until it is advanced. Indeed, amenorrhea is a common symptom in cancer treatments due to chemotherapy. Pelvic ultrasound and MRI are the imaging modalities of choice as abdominal Computed Tomography (CT) is generally contraindicated during pregnancy. Methotrexate intramuscular injection is the gold standard treatment for ectopic pregnancy. However, in situ administration may represent an alternative.

Conclusion: Ectopic pregnancy can be a rare reason for sudden amenorrhea in a patient with colorectal cancer. The latter symptom should prompt assessment of β-HCG blood levels as well as performance of appropriate imaging, if the diagnosis is uncertain.

Keywords: Ectopic pregnancy; Colorectal neoplasm; Intra uterine device

Case Presentation

A 31 year-old woman was treated since 27 months for a left metastatic colorectal adenocarcinoma, (pT3N1M+), *RAS* and *BRAF-wild*, revealed by fever related to abscessed liver metastases during post-partum period.

She had been treated by neoadjuvant chemotherapy consisting of 5-fluorouracil, leucovorin, oxaliplatin (FOLFOX regimen) plus panitumumab. Partial response had been obtained. After left colectomy for primitive tumor resection, the patient underwent right hepatectomy and left ovariectomy under laparotomy.

Metastatic recurrence occurred to the bones, liver, peritoneum 15 months after diagnosis. A new chemotherapy consisting of 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI regimen) was introduced. No tumoral response was then observed. Melena occurred, related to duodenum invasion and justifying a shift to third-line oral chemotherapy (trifluridine/tipiracil).

The important point of this case is that patient had a copper Intra Uterine Device (IUD) since two years. She was already Gravida 2, Para 2.

Amenorrhea occurred after 23 months of cytotoxic chemotherapy, with no other symptoms.

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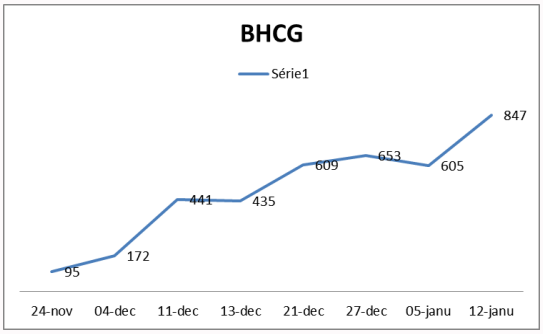

Figure 1: Biological follow up of β-HCG.

Four months later, an episode of acute abdominal pain prompted performance of blood β-HCG level, which proved positive (95IU, positivity >10 UI).

The patient was thus promptly referred to the Gynecologist.

Gynecological examination did not find any clinical signs of pregnancy. Pelvic endovaginal ultrasound showed an empty uterus with an IUD in place. There was no embryo; no pelvic mass but peritoneal fluid was present, which was interpreted as being related to the already known ascites.

The gynecologist advised to follow-up pregnancy markers as described in Figure 1. Second pelvic ultrasound performed one month later due to the increase in blood β-HCG level demonstrated signs suggestive of a right ectopic pregnancy of 20 mm in diameter. IUD was still in place.

An intra-muscular injection of Methotrexate (MTX) was performed, but β-HCG level kept on increasing (Figure 1). A second intra muscular injection of MTX (53 mg) was done six days later. β-HCG immunolabeling secondarily performed on a paraffin block of the primary colorectal adenocarcinoma was negative. Brain computed tomography ruled out the presence of brain metastasis which could have influenced β-HCG marker level.

An injection of MTX was done in situ 15 days after the first MTX injection because of the persistence of the adnexal mass confirmed by MRI (Figure 2), and because of the stagnation of β-HCG level. Introduction of gefitinib was discussed with an expert center, but patient was transferred to palliative care with hematemesis and terminal hepatic encephalopathy.

Discussion

We present a rare challenging case of pregnancy occurring during treatment of colorectal carcinoma [1-3]. Indeed, amenorrhea is a common symptom in cancer treatments due to chemotherapy [4].

HCG and sulfated hCG are hormones produced by placental syncytiotrophoblast cells and pituitary gonadotrope cells. Hyperglycosylated hCG is an autocrine hormone produced by placental cytotrophoblast cells. Hyperglycosylated hCG drives malignancy in placental cancers, and in testicular and ovarian germ cell malignancies. As discovered in 1981, most malignancies produce β-hCG or hyperglycosylated β-hCG, yet only a small proportion of malignancy cases, about 30%, have β-hCG or hyperglycosylated β-hCGβ in the blood. Their degradation product, so-called β-core fragment is present in the urine of up to 48% of cancer cases [5,6]. Furthermore, multiple case reports throughout the literature show

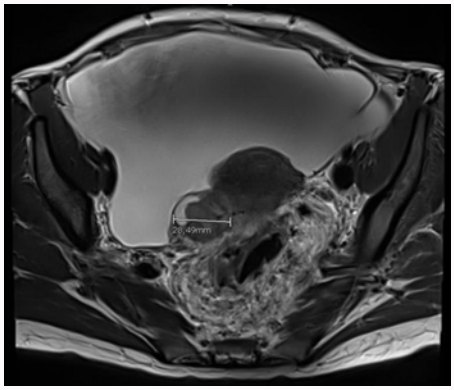

Figure 2: Pelvic MRI showing a right adnexal mass.
MRI finding an anteverted uterine (41 per 33 per 63 mm), IUD in place, a right adnexal mass (24 per 26 per 33 mm) near to the right ovarian, ascites in abundance.

that there are about 17% of positive hCG markers in colorectal cancer [7,8].

As it is known that pituitary gonadotrope cells can induce elevation of β-hCG, our patient had a brain computed tomography which did not reveal any brain lesions.

In the present case, β-hCG immunolabeling was negative, compatible with the diagnosis of Ectopic Pregnancy (EP).

EP is defined as the implantation of a fertilized ovum outside of the endometrial cavity. It accounts for approximately 1.3% to 2% of all pregnancies. The risk factors of EP include history of pelvic inflammatory disease, intrauterine device use, advanced maternal age, smoking, and a history of tubal surgery, infertility, and endometriosis or assisted reproductive technology therapy. However, it is noteworthy that risk factors can be undetected in more than half of all EP cases [9,10]. In present case, pelvic inflammatory disease due to adhesions related to peritoneal carcinomatosis as well as the presence of an IUD constituted risk factors for EP.

The most common symptoms in EP are pelvic or abdominal pain, vaginal bleeding, and amenorrhea. Our patient only had abdominal pain which could also be related to peritoneal carcinomatosis [11,12].

Extratubal ectopic pregnancies account for less than 10% of all ectopic pregnancies but are associated with greater morbidity. Surgery often is the most appropriate first-line treatment in such cases, but multiple-dose of MTX has also been used effectively [13].

MTX is a safe and effective treatment modality for patients who display appropriate criteria for surgical treatment, such in our case. The single-dose MTX protocol is the most commonly used method for selected patients with EP, and the success rate of this treatment has been reported in the literature to range between 52 and 94% [14].

Previous studies have reported that if the initial serum β-hCG values are <1500 mIU/L in unruptured tubal EP cases, routine use of MTX is not recommended, and that these cases may benefit from expectant management [14,15].

MRI is the imaging tool of choice to confirm the localization of EP. In the present case, pelvic MRI diagnosed a right adnexial mass compatible with an extratubal ectopic pregnancy (Figure 2).

In the present case, although β-hCG was under 1500 mIU/L, the gynecologists chose to administer intramuscular MTX. It has been

proved that for ovarian and abdominal pregnancies, MTX is not a first-line treatment but may be initiated when the ectopy pregnancy is initially misdiagnosed as tubal in location [15,16].

Other claims that β-hCG levels do not affect the success of MTX treatment. The American Society for Reproductive Medicine (ASRM) Guidelines also suggest that the single-dose MTX treatment regimen fails when initial serum β-hCG levels are high, and this treatment regimen is preferred over relatively low initial serum β-hCG levels [17].

So, extra uterine pregnancies with positive heart action should not be treated with MTX, therefore in our case an *in situ* injection of MTX was at least performed and an introduction of gefitinib (an orally administered EGF receptor-tyrosine kinase inhibitor) was discussed in this case of intratubal pregnancy.

Conclusion

EP can be a rare reason for amenorrhea and increase in pregnancy markers in colorectal cancer. Its diagnosis is often delayed because symptoms are unspecific until it is advanced, as amenorrhea is a common symptom in cancer treatments due to cytotoxic chemotherapy. Therefore β-hCG has to be performed in case of doubt with regards to EP in order to avoid delayed diagnosis and inefficiency of MTX injections.

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