Colon cancer in pregnancy: a diagnostic and therapeutic challenge

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Abstract
Metastatic colorectal cancer during pregnancy and postpartum is rather rare, but it represents major diagnostic and therapeutic challenges for obstetricians and surgeons. Cancer itself rarely affects the placenta or growing baby directly. However, metastatic disease is much more common than in nonpregnant patients and detecting cancer while pregnant can be complicated for both the mother and the health care team. In this article, we report a case of moderately differentiated colon adenocarcinoma in pregnancy that was diagnosed in an advanced stage, implying a complex diagnostic and therapeutic approach. The classic histological and immunohistochemical (IHC) study on this case reveals that tumorous areas have lost goblet cells and, implicitly, mucus; also, there are absent estrogen and progesterone receptors, possible causes of neoplasm in pregnancy, the rate of tumor proliferation is increased, the IHC reaction that highlights the protein responsible for cytoplasmatic anchoring of cadherins is intense positive, and the enzyme responsible for inflammation and pain is increased in these areas.

Keywords: pregnancy, colon cancer, management.

Introduction
Colon cancer in pregnancy is an extremely rare entity, resulting in an incidence according to recent studies of 0.002% [1]. The pathology is now detected during screening procedures, especially in developed countries [2]. Common clinical presentations, which raise suspicion of colon cancer and should direct the patient to the physician, include rectal bleeding, intestinal obstruction or perforation, iron-deficiency anemia, abdominal pain or changes in bowel habits.

Physical findings associated with advanced stages of disease are macroscopic rectal bleeding, palpable abdominal mass, abdominal tenderness and hepatomegaly or ascites.

Right-sided lesions usually bleed and might cause diarrhea, while left-sided tumors are identified later and may present with symptoms of bowel obstruction [3]. Since these symptoms are assessed in pregnant women, patients and physicians usually associate them to the common manifestations of pregnancy and do not seek appropriate medical evaluation [4].

Current scientific data indicates that genetic factors are greatly correlated with colorectal cancer. Moreover, environmental exposure, diet (high in animal fat or red meat, low in fibers and low overall intake of vegetables or fruits), as well as inflammatory diseases of the digestive system, are all involved in the occurrence of colorectal cancer [5, 6].

Aim
The aim of this study was to describe the interdisciplinary management of a pregnant patient diagnosed in an advanced stage with moderately differentiated colon adenocarcinoma.

Case presentation
We report the case of a 36-year-old primiparous pregnant woman (gravid 2, para 1) in the 33rd week of gestation, with previous complaints of abdominal pain, which was admitted to the Department of Obstetrics and
Gynecology, University Emergency Hospital, Bucharest, Romania, for uterine contractions. The fetus was conceived spontaneously.

The patient’s past medical and family history was negative for malignancy. She also experienced lower abdominal pain and constipation and had multiple hospitalizations for subocclusive episodes in other medical units. Also, during these admissions, she was diagnosed with elevated liver dimensions and hepatic hemangiomas.

The patient registered no history of vomiting, loss of appetite, passage of bloody or mucoid stool, jaundice, body swelling, fever or vaginal bleeding.

At the admission in our Hospital, we detected a voluminous liver that was palpable at about 20 cm inferior to the 10th rib that was smooth and tender. No other palpable masses have been identified, except to a viable singleton pregnancy estimated to be about 33 weeks’ gestation. Vaginal examination revealed a short cervix and a fetus in breech presentation. During physical examination, we also detected a severe case of scoliosis that limited the ability of the patient to rest on her back, thus contributing to the alteration of her general state.

Patient was conscious and coherent, height (H) – 1.73 m and 62 kg, pallor – present, afibrile. The patient was anemic at the time of presentation, with a hemoglobin (Hb) level of 9.2 g/dL and a hematocrit (Ht) measure of 28.3%. Other laboratory data, which included liver function tests, cancer markers and a basic chemistry panel, were pathologically modified. The liver markers were modified, registering high levels of direct bilirubin, cholesterol, fibrinogen, transaminases, an elevated white blood cell count as well as a hydroelectrolytic imbalance. We decided to test for tumor markers, which resulted to be severely elevated: \( \alpha \)-fetoprotein 56.46 IU, cancer antigen (CA) 19-9 1652.5 IU, CA 125 220.9 IU.

Furthermore, we scheduled interdisciplinary consults:

- Thoracic surgery, based on a recent episode of pleurisy, initially presumed to be due to tuberculosis, though the pleural fluid was not tested;
- Breast ultrasonography, in order to exclude a breast cancer with multiple liver metastases;
- Gastroenterology, in order to search for a gastrointestinal cancer with multiple liver metastases;
- Cardiology, in order to assess the anesthetic risks.

Following ultrasound examination, we detected large volume liver tumors (that determined severe hepatomegaly) with intense vascular signal at Doppler examination (Figure 1). A malignant process was suspected, but the primary tumor was not determined.

In order to determine the exact location of the primary tumor, a magnetic resonance imaging (MRI) scan of the abdomen and pelvis was performed. MRI examination highlighted global hepatomegaly (lesions with malignant features in the parenchyma and also thrombosis of the right branch of the portal vein suggesting a hepatocellular carcinoma rather than metastases originating from an extrahepatic source) with small amount of ascites (10 mm) surrounding the liver and right pleural effusions (1 cm thick) (Figure 2).
The patient was under close supervision, with cardiotocography monitoring each morning and regular blood tests. The pregnancy was terminated by Caesarean (C)-section at 33 weeks of gestation. An interdisciplinary surgical team composed of obstetricians and surgeons performed the intervention under general anesthesia. A single live preterm male baby, with a weight of 1750 g and an Apgar score of 8 was delivered. Placenta was located in fundal anterior position. Placenta with membranes was removed in toto. Uterine suturing was performed and hemostasis secured. During surgery, the right ovary appeared to feature malignant transformation (Figure 3).

Intraoperative frozen section examination confirmed the presence of a moderately-differentiated colonic-type adenocarcinomatous proliferation. Following the histopathological (HP) report, the multidisciplinary surgical team explored the peritoneal cavity. Peritoneal carcinomatosis was absent. The liver was severely enlarged due to multiple lesions with various dimensions located in all segments of the organ. At the level of the descending colon, 10 cm inferior to the left colic flexure a stenotic tumor was detected (Figure 4). The surgical team performed a left hemicolectomy and colo-colonic anastomosis. The surgically resected specimen was sent to the Department of Pathology in the same Clinic for HP evaluation. Due to unstable patient condition, she has been shifted to the Intensive Therapy Unit. The baby was admitted to Neonatal Intensive Care Unit (NICU) for observation and was discharged after seven days. Post-operative period was uneventful.

Subsequent examination of paraffin-embedded samples revealed strikingly similar HP features (Figure 5).

HP examination of the hemicolectomy specimen revealed a moderately differentiated (G2) adenocarcinomatous proliferation (Figures 6–8), featuring back-to-back glands, cribriform areas and small solid sheets with obvious cytological atypia, small extracellular mucin pools, as well as extensive areas of necrosis and hemorrhage. Lymphovascular invasion was present (Figure 9). The tumor was invasive into non-peritonealized pericolonic tissues (pT3), as well as two out of six lymph nodes (pN1) and metastatic to the right ovary (pM1a). In conclusion, the patient was diagnosed with a stage IVA colonic adenocarcinoma (pT3N1M1a), metastatic to the right ovary.

Histological staining with Hematoxylin–Eosin (HE), Periodic Acid Schiff–Hematoxylin (PAS–H) (Figure 10), Alcian Blue (AB) (Figure 11) and PAS–Hematoxylin–Alcian Blue (PAS–H–AB) double staining (Figure 12) for the mucus showed that at the tumor level the caliciform cell density decreased a lot. For the immuno-histochemical (IHC) study, we used a series of antibodies (Table 1).
Figure 5 – Subsequent paraffin-embedded sections confirmed the presence of an intestinal-type metastatic adenocarcinoma – detail showing an adenocarcinomatous proliferation nearby a decidual reaction (upper left) and small hyaline vessels. HE staining, ×200. HE: Hematoxylin–Eosin.

Figure 6 – Histopathological aspect of the colonic tumor showing an adenocarcinomatous proliferation with small, extracellular mucin pools (left). Normal tissue (right). HE staining, ×100. HE: Hematoxylin–Eosin.

Figure 7 – Histopathological aspect of the colorectal adenocarcinoma showing transition between malignant colonic epithelium (right) and normal tissue (left). HE staining, ×100. HE: Hematoxylin–Eosin.

Figure 8 – Histopathological aspect of the colonic adenocarcinoma showing the maximum depth of tumoral invasion and extension into pericolic tissues, featuring prominent desmoplastic reaction. HE staining, ×200. HE: Hematoxylin–Eosin.

Figure 9 – Histopathological aspect of lymph node invasion due to colonic adenocarcinoma (upper right), showing prominent desmoplastic reaction. HE staining, ×200. HE: Hematoxylin–Eosin.

Figure 10 – The mucus of caliciform cells in normal tissue is colored in intense pink (left) and in the tumor level the reaction is very low (right). PAS–H staining, ×100. PAS–H: Periodic Acid Schiff–Hematoxylin.
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Figure 11 – The mucus of caliciform cells in normal tissue is colored in blue (left), and at the tumor level the reaction is very low (right). AB staining, ×200. AB: Alcian Blue.

Figure 12 – At the tumor level, the density of mucosal cells is low. PAS–H–AB double staining, ×100. PAS–H–AB: Periodic Acid Schiff–Hematoxylin–Alcian Blue.

Table 1 – Immunohistochemical panel of antibodies used by us

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Manufacturer</th>
<th>Clone</th>
<th>Antigenic exposure</th>
<th>Secondary antibody</th>
<th>Dilution</th>
<th>Labeling</th>
</tr>
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<tr>
<td>Anti-MUC5AC</td>
<td>Santa Cruz Biotechnology</td>
<td>sc-71621</td>
<td>Citrate, pH 6</td>
<td>Monoclonal mouse IgG1</td>
<td>1:50</td>
<td>Goblet cells – mucus</td>
</tr>
<tr>
<td>Anti-MUC4</td>
<td>Santa Cruz Biotechnology</td>
<td>sc-33654</td>
<td>Citrate, pH 6</td>
<td>Monoclonal mouse IgG1</td>
<td>1:50</td>
<td>Goblet cells – mucus</td>
</tr>
<tr>
<td>Anti-Ki67</td>
<td>Dako</td>
<td>MIB-1</td>
<td>EDTA, pH 9</td>
<td>Monoclonal mouse anti-human Ki67</td>
<td>1:50</td>
<td>Cells in division in the G1, S, G2 and M phase</td>
</tr>
<tr>
<td>Anti-p53</td>
<td>Dako</td>
<td>DO-7</td>
<td>EDTA, pH 9</td>
<td>Monoclonal mouse anti-human p53 protein</td>
<td>1:50</td>
<td>Nuclear marker</td>
</tr>
<tr>
<td>Anti-CK20</td>
<td>Dako</td>
<td>Ks20.8</td>
<td>Citrate, pH 6</td>
<td>Monoclonal mouse anti-human CK20</td>
<td>1:25</td>
<td>Cellular protein of mature enterocytes and goblet cells</td>
</tr>
<tr>
<td>Anti-CK7</td>
<td>Dako</td>
<td>OV-TL 12/30</td>
<td>Citrate, pH 6</td>
<td>Monoclonal mouse anti-human CK7</td>
<td>1:50</td>
<td>Glandular epithelia</td>
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<tr>
<td>Anti-ER</td>
<td>Dako</td>
<td>1D5</td>
<td>EDTA, pH 9</td>
<td>Monoclonal mouse anti-human ERα</td>
<td>1:50</td>
<td>Estrogen receptor α</td>
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<td>Dako</td>
<td>PgR 636</td>
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<td>Monoclonal mouse anti-human PR</td>
<td>1:50</td>
<td>Progesterone receptor</td>
</tr>
<tr>
<td>Anti-CDX2</td>
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<td>DAK-CDX2</td>
<td>EDTA, pH 9</td>
<td>Monoclonal mouse anti-CDX2</td>
<td>1:50</td>
<td>Nuclear marker</td>
</tr>
<tr>
<td>Anti-β-Catenin</td>
<td>Dako</td>
<td>β-Catenin-1</td>
<td>Citrate, pH 6</td>
<td>Monoclonal mouse anti-human β-Catenin</td>
<td>1:50</td>
<td>Protein responsible for cytoplasmatic anchoring of cadherins</td>
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<tr>
<td>Anti-COX2</td>
<td>Dako</td>
<td>Cx-294</td>
<td>EDTA, pH 9</td>
<td>Monoclonal mouse anti-human COX2</td>
<td>1:100</td>
<td>Enzyme responsible for inflammation and pain</td>
</tr>
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Massive decrease of goblet cells and production of mucus at the tumor level has been demonstrated by histological and immunohistochemistry stainings. Using the antibodies anti-mucin 5AC (MUC5AC) (Figure 13) and anti-mucin 4 (MUC4) (Figure 14) for the mucus, demonstrated the absence of reactivity at the tumor level, the positive reaction having place only at normal tissue’s level. Ancillary IHC evaluation performed on the colonic tumor revealed an extremely high Ki67 proliferation index of approximately 95% (Figure 15). Tumor protein 53 (p53) is highly positive in cells in the division of the tumoral tissue and negative levels in normal tissue (Figure 16). The tumor was positive for cytokeratin 20 (CK20) (Figure 17) and negative for CK7 (Figure 18), which is a classic pattern for colorectal carcinomas and did not feature any immunoreactivity for either estrogen receptor (ER) (Figure 19) or progesterone receptor (PR) (Figure 20). The caudal-type homeobox transcription factor 2 (CDX2) revealed diffuse nuclear positivity in all tumoral cells (Figure 21), while β-catenin showed diffuse membranar and cytoplasmic reactivity across the entire specimen (Figure 22). Cyclooxygenase 2 (COX2) appears to be related to malignant tumors and it is associated with abnormal growths in the intestinal tract (Figure 23). Considering the young age of the patient (36 years), IHC evaluation of mismatch repair proteins (MLH1, MSH2, MSH6, PMS2) was also performed, but did not suggest any mutation and all markers showed diffuse nuclear positivity across the entire specimen.

After C-section in the postoperative period, the patient was transferred to the Department of General Surgery, where evolution was favorable. The patient was discharged after 14 days with good general condition, afebrile, supple abdomen, mobile with breathing, gastrointestinal transit recovered, supple postoperative wound.
Figure 13 – Positive reaction for MUC5AC in normal tissue (up), negative reaction in tumor (down). Anti-MUC5AC antibody immunolabeling, ×200. MUC5AC: Mucin 5AC.

Figure 14 – Positive reaction for MUC4 in normal tissue (left), negative reaction in tumor (right). Anti-MUC4 antibody immunolabeling, ×100. MUC4: Mucin 4.

Figure 15 – (A) Positive reaction for Ki67 revealed a high proliferation index of approximately 95%; (B) Junction area between tumoral tissue (up) and normal tissue (down). Anti-Ki67 antibody immunolabeling, ×200.

Figure 16 – Positive reaction for p53 showing tumoral cells in division. Anti-p53 antibody immunolabeling, ×200. p53: Tumor protein 53.
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Figure 17 – (A) Positive reaction for CK20 showing diffuse cytoplasmic positivity in all tumoral cells; (B) Junction area between normal (down) and tumoral tissue (up). Anti-CK20 antibody immunolabeling, ×100. CK20: Cytokeratin 20.

Figure 18 – Negative reaction for CK7 showing complete absence of immunoreactivity in the tumoral cells. Anti-CK7 antibody immunolabeling, ×200. CK7: Cytokeratin 7.

Figure 19 – This reaction showing complete absence of ERα. Anti-ERα antibody immunolabeling, ×200. ERα: Estrogen receptor alpha.

Figure 20 – This reaction showing complete absence of PR. Anti-PR antibody immunolabeling, ×200. PR: Progesterone receptor.

Figure 21 – Normal tissue (left); positive reaction of CDX2 revealed positivity in all tumoral cells (right). Anti-CDX2 antibody immunolabeling, ×200. CDX2: Caudal-type homeobox transcription factor 2.
After six days, the patient was admitted in the Department of General Surgery, University Emergency Hospital, Bucharest, for swollen edema of the lower limbs exhaled to the thighs, increased abdominal girth and size caused by ascites, shortness of breath and severe dyspnea. Paracentesis was performed. Using an 18 CH tube, 3000 mL of ascites fluid were drained abdominally. After the procedure, the respiratory function improved.

Three days later, due to complaining of progressive dyspnea, a thoracentesis as performed using a 7 Fr pleural catheter and 6000 mL of fluid/24 h were evacuated. The drainage was maintained for two days. Control radiography related that pleural liquid progresses versus the previous day and minimal right pleurotomy was performed – a 16 Fr pleural catheter was mounted.

After three days, the patient was discharged with good evolution and was referred to the Department of Oncology for palliative chemotherapy.

**Discussions**

The most frequent types of cancer occurring in pregnancy are breast and cervical cancer, hematological malignancies or melanoma, followed by thyroid cancer, lung cancer, gastrointestinal carcinoma and various types of sarcomas [7].

The diagnosis and staging work-up of pregnant mothers is unique and challenging, as colorectal cancer in pregnant women is an important hazard both the mother and the fetus. Woods et al. [8] reported that 78% of pregnancies in women with colorectal tumors resulted in live-born and healthy infants. Intrauterine death, stillbirth, prematurity or premature termination are much more frequent in these infants. Coexistence of cancer and pregnancy adds complexity to the therapeutic management of these patients [9].

Colon cancer might be hidden by the signs and symptoms of pregnancy. Abdominal pain caused by large bowel obstruction could be interpreted as normal uterine cramps, because these signs and symptoms are also found in pregnancy. Moreover, pain and anorectal bleeding may be misdiagnosed, as consequences of a hemorrhoid or anal fissure [10].

To this point, there is insufficient data for proper management of pregnant women with cancer. Guidelines are mainly based on data coming from small retrospective studies or case series with limited follow-up [3, 11].

In general, both the gynecologist and the oncologist should aim at improving the mother’s life by treating curable cancers while protecting the fetus from toxic therapeutic procedures.

The diagnostic assessment of a patient with colorectal cancer involves endoscopy with biopsy, serum carcinoembryonic antigen (CEA) levels and abdominal imaging. Endoscopy may have possible adverse effects in pregnant women, including fetal exposure to potential teratogenic medications, fetal injury secondary to maternal hypoxia, placental abruption from mechanical pressure applied to the uterus or hypotension during the procedure.

Colonoscopy in pregnancy is a relative contraindication, and the patient should be informed about the possible maternal and fetal risks [12].

Metastatic disease in general and ovarian metastasis in particular imply another challenge for the physician. The incidence of ovarian metastases related to colon cancers is higher in pregnant women (25%) than in nonpregnant ones (3% to 8%) [13, 14]. Because of this, some authors suggest prophylactic bilateral salpingo-oophorectomy concomitant with the colorectal surgical procedure. The overall outcome of pregnant women with ovarian metastases is poor, with a median survival ranging from three to 12 months.

Colonic adenocarcinoma is a rather frequent form of cancer. However, when affecting young patients or multiple family members, colonic malignancy could be related to a common germline mutation that predisposes individuals to certain types of cancer. Due to our patient’s age at diagnosis (36 years), consideration of Lynch syndrome was of primordial importance. However, the family history was not particularly striking and IHC evaluation of mismatch repair proteins (MLH1, MSH2, MSH6, PMS2) did not suggest any mutation. Microsatellite instability testing was not performed.

Mucins are high molecular weight glycoproteins, expressed by the epithelial tissue cells. They present a
high content of clustered oligosaccharides and participate in the formation of mucus with protective role in the gastrointestinal tract [15]. MUC5AC is a protein encoded by the MUC5AC gene and it is responsible for the secretion of mucus in several organs, including the intestine [16, 17]. Tumor transformation strongly influenced mucus secretion, and immunohistochemistry studies, in our case, demonstrated a dramatic decrease in tumor areas by altering the genes involved [18]. MUC4 is a transmembrane mucin encountered on normal colon epithelium and may play a prognostic role in various cancers. Overexpression of it at the colorectal level can lead to an unfavorable prognosis [19], but in the case of the patient presented, MUC4 expression is absent at the tumor level. Studies have shown that MUC4 expression may be decreased when involved overexpression of stabilized mutant β-catenin [20] and determined tumor progression [21–23].

CK20 is a cellular protein of mature enterocytes and caliciform cells, especially in the gastric and intestinal mucosa [24]. In immunohistochemistry studies, it can be used to identify adenocarcinomas with epithelial origin, normally containing CK20 protein. This protein is commonly found in colorectal cancer, transitional cell carcinomas and in Merkel cell carcinoma. It is generally used in combination with the anti-CK7 antibody to differentiate glandular tumors. CK20 is present in most colorectal cancers [25–32]. The CK20+/CK7- profile of colorectal cancers has been reported frequently in the literature [33]. CK7 is positive in simple glandular epithelium and in transient epithelium, and in IHC studies, it is used to identify ovarian cancers or transitional cell carcinomas.

The pathogenesis of colorectal cancer in pregnancy is not completely elucidated. Some scientific studies support the hypothesis that ER and PR may be involved in the carcinogenesis of colorectal cancer during pregnancy, but extensive data regarding this matter is usually scarce. The hypothesis is supported by several authors, based on the presence of receptors for estrogen and progesterone in colon cancers, as confirmed by several scientific studies [34–36]. Results show that many of colon tumors have ER and PR. These findings suggest that increased levels of sex hormones in pregnant women could stimulate the proliferation of colonic cancers, which feature these receptors. Moreover, stimulation of these receptors during pregnancy might be the consequence for advanced stages of disease found in the majority of patients at the time of diagnosis. In our case, immunostaining for ER and PR of the colon adenocarcinoma did not reveal any immunoreactivity.

Ki67 antigen is a nuclear protein associated with cell division [37], with ribosomal ribonucleic acid (RNA) transcription [38]. In this case, with the anti-Ki67 antibody, we demonstrated that at the tumor level the density of tumor cells in the division is very high, representing a biomarker of tumor aggression [39–42].

p53 plays an important role in regulating cell cycle, apoptosis and genomic stability. If the gene encoding this protein is impaired, as it is the case of malignant tumors, cell death is compromised and tumor progression becomes accelerated [43].

COX2 enzymes are known to play an essential role in the incipient sequences of pregnancy, including ovulation, decidualization, fertilization and implantation [44].

Initial events in pregnancy and the pathogenesis of tumor spread feature major similarities: both involve mechanisms that require cells to migrate from their site of origin to another location where they must establish neovascularization in order to develop and survive. Colorectal adenocarcinomatous cells express high levels of COX2 enzymes and several scientific studies revealed that COX2 inhibitors such as aspirin have the potential to alter the course of malignant progression. High levels of COX2 enzymes found in pregnant women could be involved in the pathogenesis and overall outcome of colon cancer in pregnancy.

An extremely important aspect in pregnant women with metastatic disease is involvement of the products of conception. Reliable epidemiological data regarding this aspect is scarce in the literature, because: extensive routine HP evaluation of the placenta is not always achieved, most newborns do not benefit from proper medical follow-up, malignant tumors should induce abortion and forfeit the risk of such metastases. Moreover, the majority of pregnant women with malignant tumors have localized disease without metastatic spread. Based on a quick review of medical literature, we concluded that although placental invasion is a rare phenomenon, fetal involvement is even more infrequent, accounting for one fourth of all cases with placental involvement. Metastatic involvement of the placenta or the fetus is most frequently encountered in melanoma, leukemias and lymphomas, breast cancer and lung cancer, followed by bone and soft tissue sarcomas, gynecological malignancies, gastric cancer or other tumors [45–47].

The strong positive expression of CDX2 in colorectal cancers is correlated with good prognosis [48–51], but the advanced stage of the patient and the remainder of the positive IHC markers counterbalance this prognosis. A series of studies have shown that loss of CDX2 expression in colorectal cancers is correlated with aggressive behavior [52–56].

Conclusions

Pregnant women with colorectal cancer usually have poor prognosis. The complexity of therapeutic management is dependent upon gestational age of the fetus, tumor stage and the need for emergent or elective surgery. In our case, rapid recognition of diagnosis and early chemotherapy, followed by postpartum colorectal and liver surgery may improve the outcome. Treatment of patients with malignancy during pregnancy is a subtle issue as both the patient and the fetus could be affected. The therapy should be personalized and accomplished in specialized centers with expertise, by an interdisciplinary team.

Conflict of interests

The authors declare that they have no conflict of interests.

Ethical concerns

We undersign, certificate that the procedures and the experiments we have done respect the ethical standards
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Received: January 23, 2019
Accepted: June 24, 2019