

## Case report

**GASTRIC CANCER WITH MULTIPLE METASTASES IN PREGNANCY: A CASE REPORT**

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**ABSTRACT**

The mortality rate in gastric cancer during pregnancy is very high, which dictates the need to research and improve the methods of early diagnosis of malignancies, as well as studying the pathogenesis of malignant tumors in pregnant women. We report a lethal case of gastric cancer in a pregnant woman. The findings of the autopsy, histological, histochemical and immunohistochemical examinations verified gastric signet ring cells carcinoma with multiple metastases and infiltration of the placental intervillous space. The possible pathogenesis of cancer with changes in the hormonal background occurring in pregnant women is discussed. Understanding the endocrine mechanisms of carcinoma pathogenesis will be useful for developing new therapies for gastric cancer.

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**1. Introduction**

Gastric cancer is one of the most common malignancies, ranking fourth worldwide in terms of cancer type. Despite the gradual reduction in the incidence of gastric cancer, and, consequently, the reduction in mortality rate from this type of malignant tumors among men and women, gastric cancer ranks second, accounting for 9.7% of all cancer-related deaths [1]. Gastric cancer is characterized by the significant geographical variability, showing a 15 to 20-fold difference between the highest and lowest risk regions. More than 50% of new cases are diagnosed in developing countries [2].

Depending on the cause of gastric cancer and the processes that precede its development, intestinal and diffuse types are identified. Diffuse cancer is characterized by infiltrative growth and is represented by poorly organized groups or single cells with a high content of mucin (signet ring cells). The findings of clinical observations show that an unfavorable prognosis for diffuse gastric cancer is associated with late diagnosis, rapid progress, more potential of malignant tumor cells and early metastasis [3]. Moreover, the progress of gastric cancer during pregnancy is of great interest, since it is a rare combination and is diagnosed mainly during advanced stages.

We report a lethal case of gastric cancer with multiple metastases and infiltration of the intervillous space in a pregnant woman.

**2. Case report**

The 31-year-old female patient Z. (pregnant, II ) was admitted to the Perinatal Center of the Poltava Regional Clinical Hospital from the Central District Hospital at 31 weeks of gestation and was diagnosed with Ca ventriculi T<sub>4</sub>N<sub>1</sub>M<sub>1</sub> (carcinomatosis of the abdominal cavity), post-chemotherapy status (2017) and severe anemia. The patient experienced melanorrhagia and was vomiting blood.

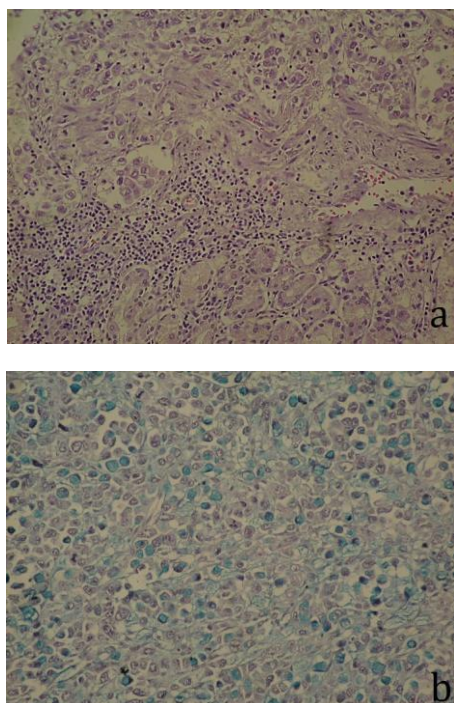
Upon hospitalization, the patient's general conditions were grave. She complained of general weakness, dizziness, nausea and was vomiting blood. The patient was subjected to clinical, laboratory and instrumental examinations.

The following procedures were performed: lower midline laparotomy, corporal caesarean section, extirpation of the uterus and uterine adnexa, exploration and drainage of the abdominal cavity. Diagnosis after surgery: pregnancy II, 31-32 weeks of gestation, cephalic presentation, fetal distress during pregnancy, placental dysfunction, Ca ventriculi T<sub>4</sub>N<sub>1</sub>M<sub>1</sub>, carcinomatosis of the abdominal cavity organs, remote metastases, ascites, post-chemotherapy status (2017), DIC-syndrome, subacute progress, phase of hypocoagulation, toxic liver damage, erosive gastritis, recurrent continuing severe gastric hemorrhage, secondary metabolic toxic encephalopathy, retinal angiopathy of both eyes, partial atrophy of cranial nerves of both eyes, chronic kidney disease-I (paraneoplastic nephropathy), chronic renal failure and severe anemia.

The postoperative fibrogastroduodenoscopy revealed an infiltrative form of Ca ventriculi and continuous bleeding. Unfortunately, the patient's clinical status progressively worsened and she developed respiratory failure and seizures, which resulted in clinical death. Resuscitation measures were not effective and biological death was confirmed.

The autopsy revealed clusters of whitish and yellowish nodules with a 3-5 mm diameter on the parietal peritoneum, on the thoracic surface of the diaphragm and the surface of the intestine's mesentery. The stomach appeared hook shaped. About 150 ml of blood clots and blood masses were found in the stomach cavity. The mucous membrane appeared with smooth folds. In the area of great curvature and the body of the stomach, the wall appeared significantly thickened to 2 cm on an area of 9x9 cm. The section presented a dense gray-white tissue and there was an ulcer with a 1 cm diameter on the surface of this area. Bloody tarry masses were found in the intestine. The liver appeared slightly enlarged and the capsule was smooth. On the liver's surface beneath the capsule, multiple whitish nodules with a 2-4 mm diameter were noted and its tissue section appeared pale brown. The gallbladder appeared pear-shaped and contained about 30 ml of dark bile; the mucous membrane appeared fine-grained and a whitish induration of 2x2x1 cm was detected at the bottom of the bladder. Biliary ducts were patent.

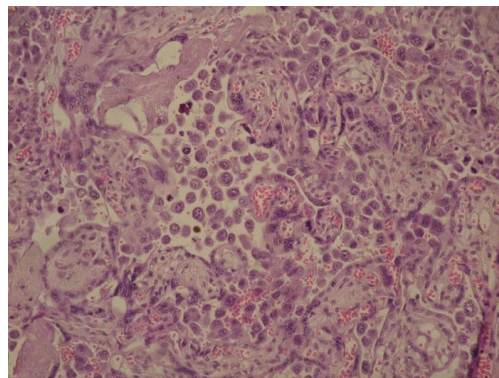
The microscopic examination of the autopsy material revealed proliferation of the signet ring cell carcinoma into all layers of the stomach wall (Figure 1a), with ulceration of the mucous membrane. Histochemical alcian blue staining revealed accumulation of mucus in the cytoplasm of the tumor cells (Figure 1b).



**Figure 1. Gastric signet ring cells carcinoma, patient Z.: a – H&E stain; b – alcian blue stain. Original magnification  $\times 100$ .**

In addition, small metastatic foci of carcinoma were found in the lung and subcapsular metastases in the liver, as well as in para-aortic lymph nodes and lymph nodes of the greater and lesser omentum and in the fatty tissue of the anterior abdominal and gallbladder walls.

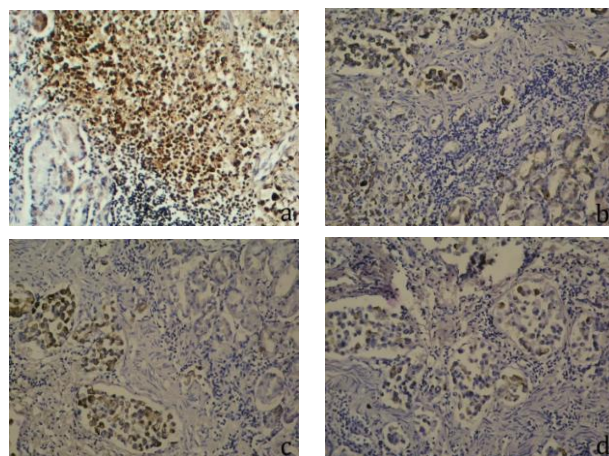
The histological examination of the postoperative material revealed carcinoma aggregations in the lumen of the cervical vessels and metastatic foci in the ovaries. Ischemic infarctions and immature type chorionic villi with uneven vascular blood filling were noted in the placental parenchyma. Fibrinoid and numerous tumor signet ring cells were detected in the intervillous space (Figure 2).



**Figure 2. Infiltration of the placental intervillous space with cells of the gastric signet ring cells carcinoma. H&E stain. Original magnification  $\times 100$ .**

The immunohistochemical examination of the primary tumor and metastatic foci revealed hyperexpression of the CEA marker (Figure 3a), moderate expression of the CK-PAN (Figure 3 b) and CK7 (Figure 3c) and selective expression of the CK20 in the single cells (Figure 3d).

The findings of the histological, histochemical and immunohistochemical studies verified gastric signet ring cells carcinoma with multiple metastases and infiltration of the placental intervillous space, which confirms the data found in the literature [4, 5]. However, the pathogenesis of gastric cancer and its relationship with pregnancy remains unclear to date.



**Figure 3. Immunohistochemical examination of the gastric signet ring cells carcinoma of the patient Z.: a – hyperexpression of the CEA; b – moderate expression of the CK pan; c – moderate expression of the CK7; d – selective expression of the CK 20. Original magnification  $\times 100$ .**

### 3. Discussion

Malignant tumors during pregnancy are reported in 0.07% - 0.1% of all malignant tumors and occur approximately once every 1000 pregnancies annually. The most common malignancies during pregnancy are melanoma, breast and cervical cancer, lymphoma and leukemia [6]. The incidence of gastric cancer in pregnancy is rare. In Japan, a country with a high incidence of this type of carcinoma, the rate of gastric cancer during pregnancy is reported to be only 0.016% [7]. The 3-year survival rate of women diagnosed with gastric cancer during pregnancy does not exceed 8%, regardless of age and stage of the illness; whereas, the 5-year survival rate is accounted for just 2.9%.

The pathophysiology of pregnancy-related cancer has not been fully understood. However, hormonal changes, immunological suppression, and increased vascular permeability and vascularization are probably the leading factors in its occurrence and progression [6].

Gastric cancer is an estrogen-dependent tumor, proved by the intensification of the malignant process during pregnancy in clinical observations. Estrogenic receptors are present in approximately 22% of cells of low-differentiated gastric cancer. Estrogenic hormones are mitogens that accelerate cell division. The mitotic effect of estrogens increases with the rise of their levels in cells and tissues of estrogen-sensitive organs and with the increase of their receptor status. In addition, estrogens increase the activity of transforming growth factor- $\alpha$ , epidermal growth factor and autocrine peptides, each of which is involved in the development of a malignant tumor process. Moreover, due to the restored form of the enzyme hydroxysteroid dehydrogenase, the activity of which is the highest in the tissues of malignant tumors, estrone is converted into estradiol, whose mitotic activity is by 5-10 times higher than estrone. Tumors also undergo enzymatic conversion by estrone sulfatase, which has no regulatory effect on mitosis, to estrone. The 4-OH and 16-OH metabolites of estrone and estradiol have a carcinogenic effect, which is ensured by genotoxic DNA damage, forming purine-free regions. In contrast to target organs such as the mammary gland, estrogenic receptors in gastric cancer seem to be a sign of tumor adaptation due to epidermal growth factor [8, 9, 10].

### 4. Conclusions

Gastric cancer during pregnancy is extremely rare and is usually diagnosed during the advanced stages. However, the mortality rate is very high when there is the combination of the two conditions, which dictates the need to research and improve the methods of early diagnosis of malignancies, as well as studying the pathogenesis of malignant tumors in pregnant women. Understanding the endocrine mechanisms of carcinoma pathogenesis will be useful for developing new therapies for gastric cancer.

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