

Bilateral Krukenberg tumor of the ovary during pregnancy

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Summary

This case report concerns a 35-year-old woman suffering from gravidic cholestasis, thrombocytosis and iterative vomiting episodes who underwent an elective cesarean section at week 35 because of recent herpetic vulvitis. Large bilateral ovarian tumors were observed which were interpreted as pregnancy luteomas. Nevertheless a biopsy of the right ovary was performed. Histologic examination revealed massive luteinization of the ovarian stroma. In addition, large tumor cells were found dispersed throughout the ovary as well as in vascular spaces as either isolated or clustered signet-ring cells. In search of the primary tumor, gastroscopy revealed a gastric ulcer in the antrum. The biopsies of the ulcer margins as well as those taken at distance demonstrated signet-ring cells in the lamina propria. Bilateral salpingo-oophorectomy and total gastrectomy were performed. In spite of postoperative chemotherapy, the patient died of disease 5 months after diagnosis.

Key words: Krukenberg tumor; Pregnancy; Massive luteinization; Luteoma of pregnancy.

Introduction

Tumor-like lesions as well as primary or secondary neoplasms of the ovary are quite infrequently diagnosed during pregnancy. Although rare, tumor-like lesions such as pregnancy luteomas, which represent massive luteinization of the ovarian stroma, are most often responsible for the bilateral ovarian enlargement [1]. Ovarian metastases associated with pregnancy have also been reported but these events as well as the finding of a primary ovarian malignancy are very unusual in this situation [2].

Gastric carcinoma associated with pregnancy is quite rare, especially in western countries. A total of 106 cases have been reported in Japan and a few additional isolated cases in other countries [3-6]. Diagnosis is usually delayed because the symptoms are attributed to the effects of the pregnancy itself and most of these reported gastric carcinomas are diagnosed in an advanced stage with distant metastases already present. The ovary is a well known metastatic site of gastric cancer, especially in the signet-ring cell type (Krukenberg tumor). Although rare, the indirect diagnosis of such a carcinoma through its ovarian metastasis is a well recognized event [7].

This report presents the case of a 35-year-old woman in whom bilateral ovarian metastases of an unrecognized gastric carcinoma were found during elective cesarean section at week 35.

Case Report

Patient history: In January 1996 this 34-year-old woman complained about epigastric discomfort. Radiologic investigations disclosed the presence of a gastric ulcer in the proximal antrum. She received antiacid therapy but abdominal discomfort persisted. Two months later no ulcer could be found at endoscopy. Biopsies taken from the gastric mucosa were normal on histologic examination.

In June 1997, the patient was sent to the hospital during the 35th week of pregnancy because of disturbed liver tests (elevated alkaline phosphatase and transaminases) and thrombocytosis (between 600 and 1200 G/l). At that time she complained about iterative vomiting episodes during the 4 last months, epigastric pain, weight loss (1 kg during the past month) and signs of virilization (hoarseness of the voice and acne). Due to worsening of the liver disease and thrombocytosis the obstetrician decided to induce labor. That same day herpetic lesions of the vulva appeared and motivated an elective cesarean section. During the operation, both ovaries were found to be considerably enlarged with a maximal diameter of about 20 cm. The clinician suspected a bilateral pregnancy luteoma and a biopsy was performed on the right ovary. Histologic examination demonstrated the presence of a Krukenberg tumor with massive luteinization (or pregnancy luteoma?) of the ovary. Testosterone level in the serum was massively elevated up to 56 mmol/l (n: 0.7-2.8 mmol/l) as well as estradiol level up to 0.6 mm/l (n: 0.1-0.4 nm/l), but dehydroepiandrosterone sulfate (DHEA-S) was normal.

Thrombocytosis persisted (1200 G/l) and liver tests were still disturbed. A gastroscopy was performed revealing a 2 cm large gastric ulcer in the proximal antrum. The biopsies of the gastric mucosa showed the presence of a signet-ring cell carcinoma. Total gastrectomy with omentectomy and left segmental colectomy together with bilateral salpingo-oophorectomy were then performed.

One month later, the patient developed an ileus because of progressing peritoneal carcinosis. Chemotherapy was attempted without success, and the patient died 5 months after the cesarean section. No autopsy was performed.

Pathology findings: The ovarian biopsy measured 4x2x2 cm. Its surface was smooth and unremarkable. The cut surface appeared homogeneous and tan. Microscopically the tissue was somewhat edematous and different cell types were present. Large cells with eosinophilic cytoplasm and moderately pleomorphic nuclei containing one or more prominent nucleoli were the most numerous. They showed a slight mitotic activity and stained positively for vimentin. Dispersed throughout these cells, obvious signet-ring cells were present with abundant foamy cytoplasm and eccentric nuclei (Figure 1). These cells stained positively with Alcian blue and were immunohistochemically positive for cytokeratin (C11), EMA and CEA but negative for CD68, thus proving their epithelial nature (Figure 2).

Revised manuscript accepted for publication September 13, 1999

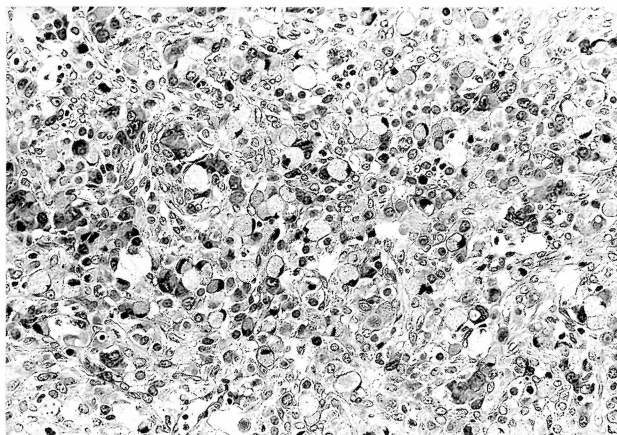


Figure 1. — Biopsy of the right ovary: numerous signet-ring cells dispersed among luteinized stromal cells with moderately pleomorphic nuclei. Original magnification 160 x.

Further, some similar cells were found in vascular spaces indicating their malignant character. The diagnosis was that of a Krukenberg tumor with massive luteinization of the ovarian stroma, the primary tumor being most probably gastric.

On macroscopic examination of the gastrectomy specimen, the borders of the gastric ulcer showed whitish tumor tissue invading the gastric wall as well as the gastrocolic ligament and the wall of the transverse colon, ulcerating its mucosa. Metastatic nodules were found in the omentum. Histologic examination showed the presence of a massively and diffusely invading gastric carcinoma predominantly of signet-ring cell type with considerable desmoplastic stromal reaction, regional lymph node metastases and peritoneal carcinosis.

Both ovaries were enlarged although smaller than at cesarean section, measuring 12.5x10x3 cm on the left side and 10.5x9.5x3 cm on the right side (Figure 2). Their surface was glistening white with some hemorrhagic areas. Microscopically, the same invading tumor cells as seen in the prior biopsy were identified. The luteinization of the stroma had regressed and had been replaced by edema.

Discussion

Tumor-like lesions as well as primary or secondary neoplasms of the ovary are infrequently diagnosed during pregnancy. According to Clement [1], a solid ovarian mass composed of large luteinized cells in a pregnant woman should be considered a luteoma unless there is convincing evidence of the contrary. The pregnancy luteoma is a non-neoplastic tumor-like ovarian lesion, often bilateral, which regresses spontaneously within days after delivery, the ovaries being normal in size a few weeks later. About a hundred cases have been reported in the literature. Usually the ovarian enlargement is incidentally discovered at term during cesarean section. In 25% of the cases, hirsutism or virilization is obvious, plasma testosterone and other androgens reaching levels up to 70 times normal values [8] as in our patient. Microscopic examination shows massive luteinization of the ovarian stroma. The cells have an abundant eosinophilic

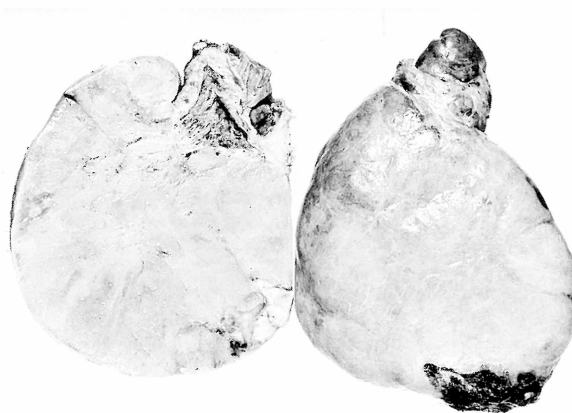


Figure 2. — Ovariectomy specimen: massive enlargement of the right ovary with smooth and glistening surface, except for prior biopsy site, and an homogenous tan-colored cut-surface.

cytoplasm with a central nucleus that may exhibit some degree of pleomorphism and hyperchromasia. Mitotic figures are usually present, some of which may be atypical [1].

Massive stromal luteinization of the ovary may also occur as a reaction to various primary ovarian neoplasms, particularly mucinous tumors. It is also a frequent finding in metastatic cancer involving the ovaries [9]. Up to 7% of all ovarian masses clinically diagnosed are actually metastases, usually from the gastrointestinal tract [7]. A case of an ovarian hemangioma associated with stromal luteinization and another one with a lymphoma have also been reported [10, 11]. Although the pathogenesis of such a stromal luteinization still remains controversial, some authors have suggested the ectopic production of HCG or other stroma-stimulating substances by the neoplastic cells [12].

In our case, the origin of the massive luteinization was most probably the result of both the pregnancy (the volume of the ovaries obviously decreased after delivery) and the presence of metastatic involvement.

Gastric cancer concomitant with pregnancy is a rare event. Only 0.4-0.5% of gastric carcinomas occur in women under 30 years of age [13]. Most gastrointestinal neoplasms diagnosed during pregnancy develop in the large bowel [14]. The first case of gastric cancer during pregnancy was reported by Fujimura and Fukuda in 1916. Since then, a total of 106 cases have been reported in Japan [3-5] and only a few isolated case reports have been published in other countries [2, 6]. The number of cases seems to be increasing, probably because the incidence of pregnancy over the age of 30 is rising.

In this situation, the major problem in diagnosis of the disease is the lack of specificity of the symptoms of gastric cancer and the frequent misinterpretation as pregnancy-related symptoms. Consequently, most of these gastric cancers are discovered in an advanced stage because of the delayed diagnosis. In the Japanese series, the diagnosis was incidental in 40% of the patients, but

there were only 3.3% of early disease, half of the tumors being unresectable at the time of diagnosis [3].

Accordingly, the prognosis of gastric cancer in this situation is extremely poor. The 3-year survival rate is 21% [3]. In addition to the delayed diagnosis, this poor outcome may also be due to biological parameters enhancing tumor growth such as the relative immunosuppression during pregnancy. Furthermore the therapeutic approach is restricted. For some authors, pregnancy and/or delivery would accelerate the progress of the disease [15].

This case raises the question whether massively enlarged ovaries presumed to represent pregnancy luteomas should be routinely biopsied when discovered. It further highlights the dramatic situation resulting from the occurrence of gastric carcinoma during pregnancy and the need to improve early detection. Gastroscopy should be performed in pregnant women with persistent gastro-intestinal complaints after the first trimester. Clinical management should be determined by the gestational age of the fetus as well as by the extent of the gastric cancer.

References

- [1] Clement P. B.: "Tumor-like lesions of the ovary associated with pregnancy". *Int. J. Gynaecol. Pathol.*, 1993, 12, 108.
- [2] Mackey J. R., Hugh J., Smylie M.: "Case report. Krukenberg tumor complicated by pregnancy". *Gynecol. Oncol.*, 1996, 61, 153.
- [3] Hiroaki U., Matsuoka H., Tamura S., Sato K., Tsunematsu Y., Kato T.: "Prognosis in gastric cancer associated with pregnancy". *World J. Surg.*, 1991, 15, 293.
- [4] Lo S. S. T., Ferguson S. A., Lee C. P., Yeung C.: "Carcinoma of the stomach complicating pregnancy". *J. Clin. Gastroenterol.*, 1996, 23, 299.
- [5] Hirabayashi M., Ueo H., Okudaira Y., Matsumata T., Hanawa S., Sugimachi K.: "Case report. Early gastric cancer and a concomitant pregnancy". *Am. Surg.*, 1987, 53, 730.
- [6] Scharl A., Huber P., Lorenzen J., Göhring U.-J.: "Gastric cancer during early pregnancy. Two case reports". *Arch. Gynecol. Obst.*, 1996, 258, 151.
- [7] Ulbright T. N., Roth L. M., Stehman F. B.: "Secondary ovarian neoplasia: a clinico-pathologic study of 35 cases". *Cancer*, 1984, 53, 1164.
- [8] Nagamani M., Gomez L. G., Garza J.: "In vivo steroid studies in luteoma of pregnancy". *Obstet. Gynecol.*, 1982, 59, 105S.
- [9] Scully R. E., Richardson G. S.: "Luteinization of the stroma of the metastatic cancer involving the ovary and its endocrine significance". *Cancer*, 1961, 14, 827.
- [10] Yamawaki T., Hirai Y., Takeshima N.: "Ovarian hemangioma associated with concomitant stromal luteinization and ascites". *Gynecol. Oncol.*, 1996, 61, 438.
- [11] Mittal K. R., Blechman A., Greco M. A., Alfonso F., Demopoulos R.: "Lymphoma of the ovary with stromal luteinization presenting as secondary amenorrhea". *Gynecol. Oncol.*, 1992, 45, 69.
- [12] Scully R. E.: "Ovarian tumors with functioning stroma". In: Haines and Taylor *Obstetrical and Gynecological Pathology*, H. Fox Ed. Churchill Livingstone, Edinburgh, 1987, 724.
- [13] Matley P. J., Dent D. M., Madden M. V., Price S. K.: "Gastric carcinoma in young adults". *Am. Surg.*, 1988, 208, 539.
- [14] Nesbitt C. J., Moise J. K., Sawyers L. J.: "Colorectal carcinoma in pregnancy". *Arch. Surg.*, 1985, 120, 636.
- [15] Furukawa H., Iwanaga T., Hiratsuka M., Imaoka S., Ishikawa O., Kabuto T., Sasaki Y. *et al.*: "Gastric cancer in young adults: growth accelerating effect of pregnancy and delivery". *J. Surg. Oncol.*, 1994, 55, 3.

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