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CASE REPORT

Krukenberg Tumor in Pregnancy: A Pathologist's Point of View

G. V. Chaitra[1], Debarshi Saha[1], Radha R. Pai[1], Mahathi Krothapalli[1]

[1]*Department of Pathology, Kasturba Medical College, Manipal University, Mangalore, Karnataka, India*

A 32-year-old female patient at 32 weeks of gestation presented with persistent agonizing epigastric pain with vomiting from conception. CA125 levels were raised and a second look ultrasound scan revealed a viable fetus with a right-sided ovarian mass. Preterm vaginal delivery at 32 weeks resulted in a viable infant. Excision of the ovarian mass revealed Krukenberg tumor (KKT). The other ovary was grossly normal. Ovarian malignancy in pregnancy is a rare phenomenon, more so is the KKT. The infrequency, initial unilaterality, and the low power view misled identification at first. Periodic acid–Schiff and mucicarmine histochemical staining clinched the diagnosis.

Key words: Krukenberg tumor, pregnancy, CA125, E-cadherin

INTRODUCTION

According to Woodruff and Novak, Krukenberg's original criteria for this eponymous tumor were (i) tumor in the ovary, (ii) signet ring cells indicating intracellular mucin production, and (iii) sarcoma-like infiltration into the ovarian stroma.[1] Stomach is the primary site in 70%, but metastases from the colon, appendix, and lobular breast carcinoma are also common.[2] Adnexal tumors are found in 0.16%–0.04% of pregnancies, and of these, 1%–3% are malignant.[3] A recent report of 2014 that mentions publication of only eight cases of Krukenberg tumor (KKT) witnessed in the last 5 years identifies the uniqueness of KKT in pregnancy.[4] The reason for their preponderance in young patients is possibly germline mutation of the E-cadherin gene that predisposes these individuals to develop diffuse gastric carcinomas at earlier age.[5] We report a case of unilateral KKT in a 32-year-old pregnant woman at 32 weeks of gestation, the origin of which was unknown at the time of diagnosis.

CASE REPORT

A poverty-stricken 32-year-old primigravida presented at 32 weeks of gestation with moderate to severe, nonradiating epigastric pain apparently without any obvious relieving factor, including H2 blockers.

On examination, she was afebrile and had a pulse rate of 86/min, blood pressure of 128/88 mmHg, and PO_2 was saturated well in room air. An initial ultrasound assessment divulged a normal intrauterine pregnancy and another distinct mass to the right of the uterus presumed, subserosal fibroid. Abdominal examination revealed a gravid uterus at around 31 weeks of gestation, mild epigastric tenderness, and mass from midline to right flank. CA125 was found elevated to 283.7 U/ml and lactate dehydrogenase, 1262 U/L.

A repeat ultrasound scan revealed an adnexal mass of heterogeneous echodensity of approximately 18 cm in largest diameter distinct from the uterus, now presumed ovarian neoplasm.

An active preterm labor at 35 weeks of gestation yielded a viable infant through vaginal delivery. The infant was 1.3 kg at birth, with APGAR scores of 9/10 both at 1 and 5 min.

One month after delivery, an exploratory laparotomy disclosed an enlarged ovary measuring 20 cm × 15 cm with intact capsule. The left ovary grossly appeared normal. Right-sided salpingo-oophorectomy and infracolic omentectomy were performed.

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Corresponding Author: Dr. Debarshi Saha, Department of Pathology, Kasturba Medical College, Manipal University, Light House Hill Road, Mangalore - 575 001, Karnataka, India. Tel: +91-824-2422271 (extension 5553); Fax: +91-824-2424183.
E-mail: devrishi2006@gmail.com

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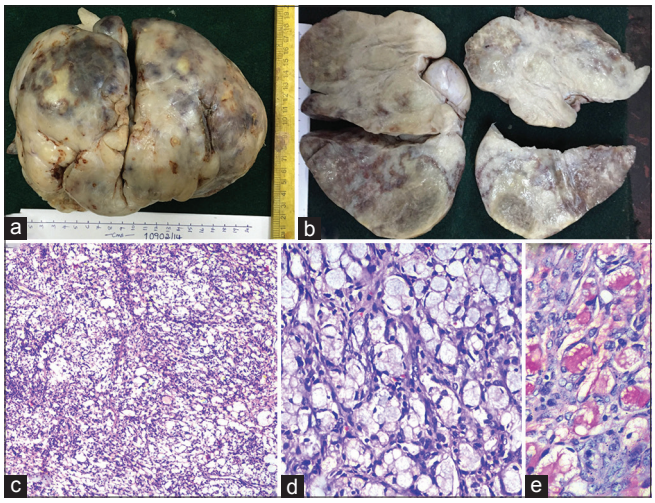

Figure 1: (a) Right ovary, boll elated but overall maintaining shape, no breach of capsule. (b) Cut surface, mucoid, and solid areas. (c) Low power – diffuse arrangement of cells and semblance of microcysts, H and E, ×100. (d) High power – signet ring cells in diffuse arrangement, H and E, ×400. (e) Mucicarmine stain: showing the mucin in the signet ring cells

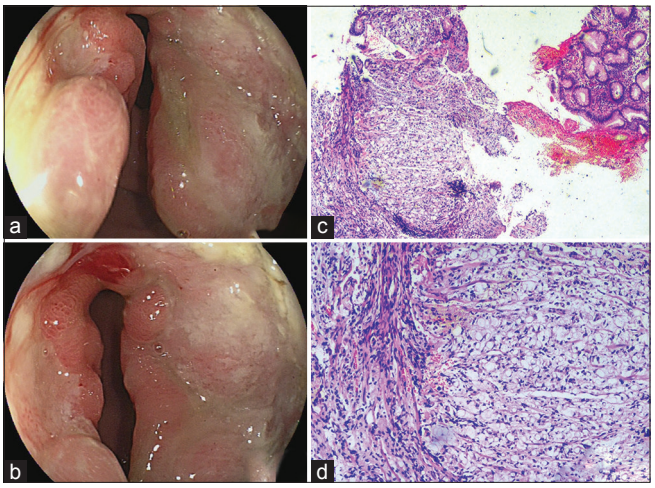

Figure 2: (a and b) endoscopic view of stomach showing nodular ulcerated growth in the gastric wall partially obstructing lumen. (c) Gastric foveolar epithelium and tumor composed of sheets of signet ring cells in the deeper mucosa and submucosa, H and E, ×100. (d) The tumor composed of signet ring cells, H and E, ×400

The right ovary was enlarged, measuring 21 cm × 15 cm × 8 cm, with intact capsule, smooth exterior surface maintaining its normal shape [Figure 1a]. Its cut surface was lobulated, grayish-white, and glistening [Figure 1b]. Microscopic examination revealed replacement of ovarian architecture by tumor cells containing enlarged, hyperchromatic, irregular nuclei arranged in sheets punctuated by microcystic spaces, not unlike the reticular variant of yolk sac tumor (YST) [Figure 1c]. The tumor cells with abundant clear cytoplasm contained a single large vacuole coercing an irregular hyperchromatic nucleus to the periphery [Figure 1d]. Periodic acid–Schiff (PAS) and mucicarmine stain demonstrated brightly pink staining substance within their cytoplasm [Figure 1e]. A diagnosis of KKT was suggested. Omental portion sent to histopathology was free from tumor involvement even with meticulous examination.

A search for the primary source was undertaken. Gastroscopy was the investigation of choice since the omnipresent gastrointestinal symptoms continued its detriment on the patient effecting a relentless weight loss. A focally ulcerated lobulated tumor mass narrowed the gastric lumen [Figure 2a and b]. Biopsy morphology from the deep-seated tumor matched that of the ovary. Mostly, the tumor occupied the submucosa, infiltrated into the deeper layers, and extended to broad foci in the mucosa expanding the lamina propria without involving the foveolar glands [Figures 2c and d]. The patient, now fully aware of her predicament and penury, forbade any attempts to treat her.

DISCUSSION

Certain aspects of this tumor posed diagnostic difficulties to the pathologist. The deceptive unilaterality did not favor a KKT at the outset since more than 80% of the KKTs were bilateral.[2] Moreover, the low power microscopic appearance coupled with the characteristic young age of the patient furthermore buttressed our opinion of YST. It was at higher power that "YST" generated misgivings. YST may contain cells with clear cytoplasm, but the characteristic signet rings are never noted. Moreover, YST cell cytoplasm may stain with PAS due to glycogen content but never with mucicarmine since mucicarmine stains acidic sialomucins.

Discriminating from other differentials was easy. Primary mucinous surface epithelial adenocarcinomas usually have an older age of preponderance[6] and alter the shape of the ovary. Architecturally, they exhibit papillae and tubule/gland formation. Metastatic mucinous carcinoid shows tumor cell aggregation and rosette formation even if present at an occasional focus; sarcoma-like infiltration should not be observed. Immunohistochemistry with chromogranin, synaptophysin, and neuron-specific enolase gives the definite verdict. Clear cell carcinoma is surface epithelial tumor, arises at older age, and alters the shape of the ovary. Papillary and tubulocystic patterns should be found with hobnail cells lining the cysts and mononuclear inflammatory infiltrate.[6] The mucicarmine-negative, PAS-positive glycogen imparting the clarity to cells should also be diastase labile.[2,6]

Signet ring-stromal tumors are rare, unilateral tumors and stain negatively for PAS or mucicarmine since cytoplasmic

edema or mitochondrial swelling induces the transparency.[7] Sclerosing stromal tumor,[2] particularly at low power, demonstrates a lobular architecture, rich capillary meshwork. They often contain lipid in the cytoplasm,[7] so PAS and mucicarmine should stain negatively.

Retrograde lymphatic permeation rather than peritoneal seeding is the mode of spread from the gastric region to the ovaries.[2] Since the woman was gravid, altered venous and lymphatic circulation may have abetted this particular mode of metastasis. Hence, the attached peritoneum and omentum were free from tumor deposits.

The CA125 below 35 U/mL is generally accepted as the upper normal limit though levels >16 U/mL are argued as better performing in ovarian malignancy detection, yet with low sensitivity and specificity.[8] In addition to ovarian cancers, gastrointestinal, liver, endometrial, lung, and breast carcinomas also express higher levels of CA125 along with benign uterine, liver, and gastrointestinal diseases. Its utility, paradoxically, is excellent in managing postoperative ovarian cancers.[8] CA125 levels in the present case were 283.7 U/mL, and lower than that found in surface epithelial-stromal tumors (346 U/mL), but much lower than that of serous adenocarcinoma (560 U/mL).[9] Serous carcinomas, particularly at high grades, largely churn out CA125 in thousands.[9] Thus, CA125 levels in our case obviated any possibility of serous surface adenocarcinoma. Other malignant surface epithelial-stromal tumors were too, less likely.

E-cadherin gene loss-of-function mutation is well known phenomenon in lobular breast carcinoma and also seen in diffuse gastric carcinomas, both of which are implicated in KKT. It is tempting to generally hypothesize that E-cadherin gene is mutated in KKT regardless of the primary source but needs a larger contextual study to marshal unequivocal evidence in its favor.

Thus, KKT is occasionally seen in pregnant women. Unilateral KKTs pose additional diagnostic challenges. It has to be distinguished from mucinous and clear cell carcinomas, signet ring and sclerosing stromal tumors, and metastatic mucinous carcinoid. Histochemical stains, PAS, and mucicarmine are instrumental in diagnosis. A moderately raised CA125 level is expected but does not indicate the nature of the tumor. The origin has to be sedulously sought out, which largely is the diffuse gastric carcinoma. Loss of function of E-cadherin gene is an interesting proposition in the etiology of these tumors but needs to be proved by a larger study.

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Conflicts of interest

There are no conflicts of interest.

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