Renal cell carcinoma treatment during pregnancy: Histopathological findings suggestive of rapid tumor growth

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Abbreviations & Acronyms
CS = caesarean section
HA = hand assisted
Lap. = Laparoscopic
N/A = not available
PN = partial nephrectomy
RAPN = robot-assisted partial nephrectomy
RCC = renal cell carcinoma
RN = radical nephrectomy

Introduction: Diagnosis of renal cell carcinoma during pregnancy is rare. We report a case of renal cell carcinoma during pregnancy with rapid growth.

Case presentation: A 39-year-old woman presented to our hospital for treatment of renal tumor at 22 weeks gestation. The tumor had a cystic lesion with a partition and showed rapid growth from 28 mm to 32 mm over a period of 4 weeks. The tumor was diagnosed as renal cell carcinoma and an open partial nephrectomy was scheduled at 26 weeks gestation. The operation and perioperative course were successful. Pathological findings confirmed the tumor to be clear cell renal cell carcinoma with G2 > G3, Fuhrman grade 2, pT1a, negative surgical margin, and positive detection of progesterone receptor.

Conclusion: We reported the successful management of a patient who was diagnosed with renal cell carcinoma during pregnancy. We also had a suggested association between rapid growth tumor and progesterone based on histopathological analysis of the tumor.

Key words: partial nephrectomy, pregnancy, progesterone receptor, renal cell carcinoma.

Keynote message
We experienced the successful management of a patient with RCC during the antenatal period. The association between rapid tumor growth and progesterone receptor based on histopathological analysis of the tumor was suggested.

Introduction
Although a diagnosis of cancer during pregnancy is rare, approximately one in every 1000 pregnant women is diagnosed with cancer during the prenatal period.1 Among urological tumors, RCC is the most common during pregnancy.2 We describe a case of RCC during pregnancy and speculate about rapid growth of the tumor, based on unique pathological findings.

Case presentation
A 39-year-old woman presented to the former hospital due to abnormal findings in her right kidney during an ultrasound on a physical examination. At the time, she was 18 weeks pregnant. The ultrasound findings comprised a heterogeneous, well-demarcated mass at the middle pole of the right kidney with an approximate diameter of 28 mm (Fig. 1a). Magnetic resonance imaging revealed a multifocal cystic renal mass at the middle pole (Fig. 1b). The initial treatment plan was observation, followed by resection after birth. However, the tumor increased in size by 4 mm over a period of 4 weeks (Fig. 1c). Thus, the patient was recommended to undergo resection, and was referred to our hospital.

Fine-needle biopsy was performed to rule out benign tumors, such as mixed epithelial and stromal tumors. The pathological diagnosis was RCC. As the tumor showed definite growth, we chose...
to perform resection after discussion with the patient, as well as our anesthesiology and obstetrical services. At 26 weeks’ gestation, right open PN was performed. We chose a retroperitoneal approach in the left lateral position with fetal monitoring because we thought it to be important to perform the procedure safely in a conventional procedure. If symptoms of premature labor were observed in association with the operation, administration of a uterine contraction inhibitor was considered. The surgery was successfully completed without any problems for the patient or fetus. Compared to typical PNs, the vessels around the kidney were well-developed; thus, more careful manipulations were needed. The patient recovered well and was discharged on postoperative day 5. Pathological examinations showed clear cell RCC, G2-G3, Fuhrman grade 2 (Fig. 2b) with progesterone receptor expression and without estrogen receptor expression (Fig. 2c). The patient delivered her baby naturally without further complications at 40 weeks’ gestation.

Discussion

To date, there have been 24 reported cases of RCC during pregnancy (Table 1). Generally, young people exhibit translocation RCC, but the manifestation differs in pregnant patients, such that most reports of RCC during pregnancy have been the clear cell type. In these past cases, surgeries were performed in early pregnancy and the sizes of the tumors have all been >4 cm. In 21 of 24 cases (88%), RN was performed, with eight cases (33%) receiving laparoscopic surgery.

Several considerations are needed for pregnant patients with RCC. First, radical or PN must be chosen. Second, the approach should be determined: open, laparoscopic, or robotic. Although minimally invasive approaches are becoming more standardized, it is important to assess individual conditions, such as gestational week, abdominal status, the
effects of pneumoperitoneum on the fetus, and tumor status (size, position, and growth speed).

If surgery is deemed necessary during pregnancy, collaboration with obstetricians and anesthesiologists is needed. Regarding anesthesia, close attention is needed to avoid hypoxia, hypotension, and the use of nonsteroidal anti-inflammatory drugs. Notably, extended hypoxia and hypotension can lead to fetal death. Regarding obstetrics, it is important to plan for possible emergency delivery of the fetus, depending on the outcome of surgery.³

Regarding the timing of resection, it can be performed safely in the first trimester for patients who are diagnosed early. Surgeries during the second and third trimesters require additional precautions to prevent uterine contractions. Uterine manipulation and hypotension should be avoided because these negatively affect uteroplacental perfusion during this period.³ Buda et al. postponed RCC resection until 28 weeks’ gestation (threshold of lung maturation).⁴ In the present case, the tumor showed particularly rapid growth; thus, we thought that surgery was needed, despite the pregnancy.

RCC in pregnant patients seems to be heterogenous; each patient demonstrates differences in tumor size, status, and growth. Appropriate treatment options should be discussed with patients. Even with a plan of observation, careful follow-up is needed with frequent ultrasound examinations to check whether the tumor shows rapid growth.

As for the rate of growth, Chawla et al. reported a mean growth rate of 0.28 cm/year in a meta-analysis of 286 renal masses at a median follow-up of 32 months.⁵ This case showed faster growth than this average speed. We were concerned that this rapid growth was derived from tumor aggressiveness. When we planned the postnatal surgery, it could be estimated up to more than 50 mm at the end of pregnancy. However, clear cell RCC even with grade 2–3 usually is less likely to demonstrate 4 mm growth within 4 weeks. We supposed to the relationship between pregnancy and the tumor rapid enlargement.

There might be two reasons for the rapid growth of the tumor in the present case. First, the volume of circulating blood increases during pregnancy, which may influence tumor growth. Consistent with this, intraoperative findings of blood vessels revealed greater dilation than that typically observed. Second, changes in the levels of estrogen and progesterone during pregnancy could aid tumor growth. In general, estrogen and progesterone reach to a high peak during pregnancy. However, clear cell RCC even with grade 2–3 usually is less likely to demonstrate 4 mm growth within 4 weeks.

Regarding tumor aggressiveness, there have been no report about the histopathological finding between estrogen/progesterone receptor expression and RCC. Although several reports support that the change of estrogen and progesterone level and RCC are controversial,⁶–¹¹ several reports support that the change of estrogen and progesterone was related to the growth of RCC.⁶–¹⁰ However, to our knowledge, there have been no report about the histopathologically proven finding between estrogen/progesterone receptor and RCC.

In this case, we performed histopathological evaluation of estrogen and progesterone receptor expression with the hypothesis that the interaction with hormonal change and receptor expression in the tumor would affect the tumor growth. This could have contributed to the rapid tumor growth in this case. However, further studies are needed to confirm our hypothesis.

### Table 1  Details of cases in which pregnant patients were diagnosed with RCC

| Reference       | Year | Age | Laterality | Tumor size | Treatment | Pathology          | Mode of delivery       |
|-----------------|------|-----|------------|------------|-----------|--------------------|------------------------|
| O’Connor et al. | 2004 | 34  | Lt.        | 3.5 cm     | Lap.RN    | N/A                | Spontaneous delivery   |
| Sainsbury et al.| 2004 | 30  | N/A        | N/A        | Lap.RN    | N/A                | Spontaneous delivery   |
| Ceglowska et al.| 2006 | N/A | Rt.        | N/A        | RN        | N/A                | CS at the 38th week    |
| Van Vasten et al.| 2006 | 30  | Lt.        | 6.5 cm     | Lap.RN    | Clear cell type    | N/A                    |
| Casella et al.  | 2007 | N/A | Lt.        | N/A        | RN        | N/A                | N/A                    |
| Stroup et al.   | 2008 | 52  | Lt.        | 6 cm       | Lap.RN    | Clear cell type    | CS at the 33rd week    |
| Simon et al.    | 2008 | N/A | Rt.        | N/A        | RN        | N/A                | CS at the second trimester |
| Van der Veldt et al.| 2008 | 20  | N/A        | N/A        | N/A       | N/A                | N/A                    |
| Lee et al.      | 2008 | 39  | N/A        | 14.5 × 12 × 17 cm | Lap.RN    | Clear cell type    | Spontaneous delivery   |
| Buda et al.     | 2008 | N/A | N/A        | N/A        | N/A       | N/A                | CS at the 26th week    |
| Sung Yul Park et al. | 2008 | 36  |Lt.         | 3.8 cm     | RAPN      | Conventional type  | N/A                    |
| Fynn et al.     | 2009 | 33  | Rt.        | 12 × 14 cm | RN        | N/A                | CS at the 26th week    |
| Bovio et al.    | 2009 | 20  | N/A        | 5.5 × 4.5 × 3.5 cm | RN        | Xp11.2 translocation | N/A                   |
| Pearson et al.  | 2009 | N/A | Rt.        | N/A        | RN        | N/A                | CS at the 26th week    |
| Stojnic et al.  | 2009 | 22  | N/A        | N/A        | RN        | N/A                | N/A                    |
| Armar et al.    | 2010 | 26  | Rt.        | N/A        | RN        | N/A                | CS at the 34th week    |
| Betz et al.     | 2011 | 28  | N/A        | 9.3 cm     | RN        | N/A                | CS at the second trimester |
| Yin et al.      | 2013 | 32  | N/A        | N/A        | Lap.RN    | N/A                | Spontaneous delivery   |
| Katayama H et al.| 2014 | 46  | N/A        | N/A        | RN        | N/A                | CS at the 26th week    |
| Zsolt Donján et al.| 2014 | 32  |Lt.         | 6.1 × 4.1 cm | HALap.RN  | Chromophobe cell type | Spontaneous delivery |
| Daniel Ramirez et al.| 2016 | 35  |Rt.         | 7.5 cm     | RAPN      | Chromophobe cell type | Spontaneous delivery |
| Murat Binbay et al.| 2016 | 34  | Rt.         | 6 × 6.5 × 6.5 cm  | Lap.RN    | Clear cell type    | CS at the 36th week    |
| Efe C Ghnney et al.| 2017 | 37  | Rt.         | 7.1 × 11 cm  | RN        | Clear cell type    | CS at the 30th week    |
| Ercan et al.    | 2018 | 36  | Rt.         | 12 × 9 cm   | RN        | N/A                | CS at the 38th week    |
| Present case    | 2018 | 39  | Rt.         | 3.5 × 3 × 3 cm | PN        | Clear cell type    | Spontaneous delivery   |
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Conflict of interest

The authors declare no conflict of interest.

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