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Renal Cell Carcinoma in a Pregnant Woman with Horseshoe Kidney

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ABSTRACT

Kidney cancer is rare during pregnancy; to our knowledge, this is the first reported case of renal cell carcinoma in horseshoe kidney diagnosed in the second trimester of pregnancy. We performed open radical nephrectomy when the pregnancy was completed. (J CANCEROL. 2016;3:18-21)

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Key words: Clear cell carcinoma. Horseshoe. Nephrectomy. Pregnancy.

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INTRODUCTION

Cancer during gestation is a rare phenomenon with an incidence of 1:1000 pregnancies, approximately[1]. The most frequent tumors that affect pregnant women are cervical cancer, breast cancer, lymphomas, and acute leukemias and melanoma. Less common malignancies are gastrointestinal, urological, and lung cancers[2].

Renal cell carcinoma (RCC) is the most common urological cancer during pregnancy, followed by bladder cancer and adrenal tumors, especially pheochromocytoma. Ureteral and urethral malignancies and other malignancies that involve the urinary tract are rare during pregnancy[3].

We present kidney tumor found in a pregnant woman.

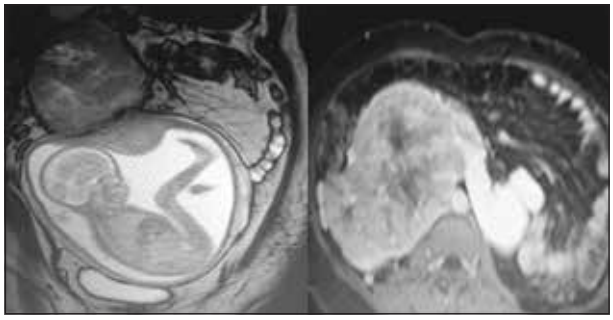

Figure 1. Magnetic resonance imaging of horseshoe kidney with renal tumor on the right side.

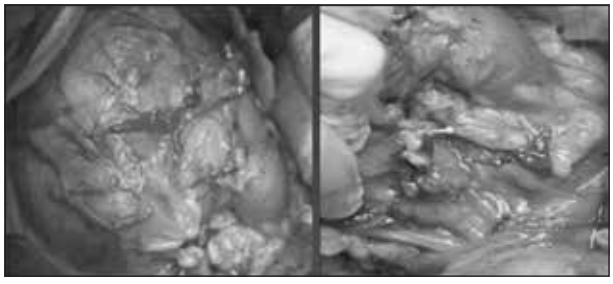

Figure 2. Tumor on the horseshoe kidney during the surgery.

CASE REPORT

A woman aged 37, gravida 4, para 3, was referred to our hospital by an obstetrician who had diagnosed a mass in her right kidney at gestation week 26. She had a previous history of hypertension and gestational diabetes mellitus. The mass has been detected after onset of hematuria and urinary tract infection during the second trimester. Blood count, urea, creatinine, and electrolytes were normal. Renal ultrasonography revealed an 8 cm solid mass, heterogeneous echotexture, arising from the mid-to-lower pole of the right kidney. To assess the nature of the mass further, magnetic resonance imaging (MRI) was performed and showed right solid, heterogeneous renal mass in the lower pole and middle upper pole of horseshoe kidney. There was no evidence of surrounding soft-tissue invasion, of retroperitoneal lymph node enlargement, or inferior vena cava (IVC) infiltration (Fig. 1).

The patient's hematuria resolved spontaneously. After discussion with the patient, it was decided to adopt a conservative approach to management until delivery. She continued the pregnancy until 35 weeks' gestation; a 2,150 g boy was born with Apgar scores of 9 at one minute and 9 at five minutes.

The woman underwent a right radical nephrectomy at four weeks after cesarean section. Surgery was performed through a midline transperitoneal incision.

After mobilization of the right colon and duodenum, the horseshoe kidney was exposed; the right ureter was dissected off the mass (Fig. 2).

The right renal hilum was exposed and divided. The isthmus was divided and the remaining portion was closed with running suture (Fig. 3).

The operative time was two hours. The estimated blood loss was 1,500 cc, the patient required transfusion of three units of packed red blood cells. She experienced severe hypertension during initial

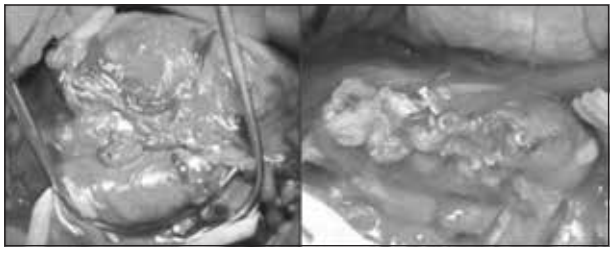

Figure 3. Suture isthmus.

postoperative recovery, so she was treated with alpha methyldopa 50 mg every eight hours, hydralazine 50 mg every six hours, and nifedepine 20 mg every 12 hours. Postoperative hemoglobin concentration was 10.5 g/dl, hematocrit 32%, leukocytes 8.2 x 10^3/µl, platelet count nadir was 169 (10^3/µl), lactate dehydrogenase 600 µl/, creatinine 0.83 mg/dl, normal liver enzymes.

She was discharged postoperatively after five days with indication of nifedepine 20 mg every eight hours.

Histopathological examination revealed clear-cell renal carcinoma, Fuhrman grade 2 with maximum diameter of 14 cm, there was no invasion of the renal capsule, and with necrosis. Pathological staging was T2b, Nx, M0.

DISCUSSION

Cancer in pregnancy seems be more common over the last 30 years, the main reason being the increasing number of women bearing children at an older age[2]. Despite the current tendency of women to bear children at more advanced ages, renal malignancies are rarely diagnosed during pregnancy; approximately 102 cases have been reported in the medical literature[4].

The incidence of RCC in in pregnant women is only partially explained by increasing maternal age; in a study in Sweden, there was positive association between parity and the risk of renal cancer: compared to nulliparous women, the risk was nearly two times higher in women with five or more live births[5].

The risk of renal cancer in pregnancy could be explained by three mechanisms[6]: (i) an increment in body mass index and increased risk of hypertension and diabetes are factors for the development of renal malignancy; (ii) pregnancy is characterized by new tissues and vascular structure and the associated increase in angiogenesis might have a role in the genesis of RCC[6,7]; (iii) there is, in an animal model, evidence of association between estrogen and progesterone on renal cancer.

Pregnant women can present typical symptoms of renal cancer or be diagnosed incidentally on routine abdominal ultrasound.

In a recent review, Boussios and Pavlidis found that the primary presentation of RCC in pregnancy was pain and hematuria, while the triad of pain, palpable mass, and hematuria was present in 26% of cases, followed by hypertension in 18% of patients[4]. Symptoms of RCC, such as pain, hematuria, and hypertension during gestation, may mimic symptoms of common pregnancy related disorders. Hematuria in pregnancy is usually due to non-neoplastic causes. Hypertension, as a symptom of RCC in pregnancy, represents a diagnostic dilemma because hypertension is often seen in pregnancy and may mimic pre-eclampsia[4]. Obstetricians in the presence of loin and abdominal pain, hematuria, or hypertension must keep in mind a diagnostic evaluation with a full abdominal ultrasound to allow early diagnosis of malignancies.

Evaluation of hematuria in pregnant women includes urinalysis, urine culture and cytology, abdominal ultrasound, and cystoscopy. An MRI without contrast can be performed when ultrasound is non-diagnostic. In cases of indeterminate masses, diagnosis can be performed on the basis of ultrasonography guided biopsy; if the mass is

inflammatory or benign, the pregnancy can be continued with close radiological follow-up[7].

The standard treatment reported in series cases was open radical nephrectomy, nephron-sparing surgery, and laparoscopic approach in few patients[4].

There are several practical considerations when treating RCC in pregnancy.

The safety of the mother should always be a priority, though management must take into account her wishes regarding the health of the unborn child.

The timing of surgery depends on the biological behavior of the tumor and neonatal survival rates for different gestations.

The average growth of RCC is 0.28 cm per year, and tumor doubling time is around 300 days, 72 weeks[6,7]. The majority of small renal masses have a slow growth rate and do not need urgent intervention, and can be safely observed until the pregnancy is completed or up to 28 weeks[6]. However, a case has been described of a fatal fast-growing RCC diagnosed in the second trimester of pregnancy and increasing threefold in size over 14 weeks[8].

When surgery is performed during the first trimester, there is increased risk to the life of the fetus, whereas surgical treatment in the second and third trimester is considered to be reasonable and safe after careful consideration of the mother and fetus[6]. In our case, we think that it is advisable to continue the pregnancy.

CONCLUSION

Kidney cancer is rare during pregnancy and the symptoms can mimic urinary infection. The diagnosis and its management can be a challenge.

To our knowledge, this is the first reported case of RCC in horseshoe kidney diagnosed in the second trimester of pregnancy. We performed open radical nephrectomy when the pregnancy was completed.

DECLARATION OF INTEREST

None of the contributing authors have any conflict of interest, including specific financial interests or relationships and affiliations relevant to the subject matter or materials discussed in the manuscript

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Epidemiology of Triple-Negative Breast Cancer in Peru

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ABSTRACT

In recent decades many reports have described the epidemiology and molecular biology of triple-negative breast cancer; however there is little information about the epidemiology in Latin American countries such as Peru. In this review we present clinical and epidemiological data published in national and international literature about this malignancy in Peruvian patients. (J CANCEROL. 2016;3:22-7)

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INTRODUCTION

Breast cancer is a public health problem in the world where more than 500,000 women die because of this disease each year. Despite the great progress in the last decade, breast cancer still holds mysteries in its biology.

In the year 2000, knowledge about the biology of breast tumors changed radically because it was shown that the clinical and biological behavior of this disease was explained by its gene expression, where its evaluation makes it possible to classify this neoplasia in four major subtypes, corresponding to luminal A, luminal B, HER2-enriched, and basal type[1,2]. Determination of the molecular subtypes of breast cancer is performed using cDNA microarrays; further studies could demonstrate that immunohistochemical studies with a set of markers (ER, PR, HER2, CK5/6, EGFR) permit to obtain a surrogate of these molecular subtypes with a high correlation with patients prognosis[3].

Triple-negative breast cancer (TNBC) represents a heterogeneous group of tumors with a lack of significant expression of estrogen, progesterone, and HER2 (the three most important markers in breast cancer), and actually is a exclusion criteria that groups tumors with different clinical behaviors[4,5]. The main clinical feature of TNBC is its aggressiveness, with higher rates of distant metastases compared with other subtypes of breast cancer, where visceral metastasis (liver, lung, and central nervous system) is frequent, with early recurrences and increased risk of death[6].

Recent molecular studies have reported that TNBC is actually a group of six different diseases that differ in their clinical behavior, sensitivity to chemotherapy, and survival[7]. These subtypes are:

- Basal type 1: Presents overregulation of genes involved in processes of cell cycle, DNA repair, and cell proliferation.
- Basal type 2: Mainly driven by signaling growth factors (EGFR, MET, Wnt, and IGF1R).
- Immunomodulatory: Overexpress genes involved in processes of cellular immunity (medullary breast cancer).
- Mesenchymal: Present related regulation of cell motility, cell differentiation genes, pathways, and receptors that interact with the extracellular matrix.
- Mesenchymal stem like: Share similar biological processes with mesenchymal subtype, but also involve growth factor signaling and are enriched with genes associated with epithelial-mesenchymal transition (metaplastic cancer).
- Luminal androgen receptor: Genes related to androgen receptor signaling (AR, DHCR24, ALCAM, FASN, FKBP5, APOD, PIP, SPDEF and CLDN8).

In table 1 we present a comparison between distinct subtypes. In this review article we describe the characteristics of this disease in the Peruvian population from a number of publications found in the scientific literature.

SOCIODEMOGRAPHIC AND EPIDEMIOLOGICAL ASPECTS OF THE PERUVIAN POPULATION

Peru has an estimated population of 30.8 million inhabitants, with a similar proportion of men and women[8]. With an annual GDP of $203.8 billion dollars, health expenditure corresponds to only 4.8%[9]. Data from the GLOBOCAN 2012 project described an incidence of about 43,000 new cases each year. The most common cancers in women are cervical cancer (age-standardized rate of 32.7 per 100,000 women) and breast cancer (28 per 100,000 women)[10]. Cancer care in Peru is carried out by the Ministry of Health, Social Security, Armed Forces Hospitals, and Private Clinics.

Table 1. Comparison of the characteristics of triple-negative tumors with other breast cancer subtypes

Features	Triple-negative	Luminal A	HER2 amplified
Demography	Higher incidence in African Americans and Hispanics than in Caucasians	Higher in Caucasians and Asians (> 70%)	Higher incidence in Asians and Hispanics than in Caucasians and African Americans
Epidemiology	Peru 21.3%; Mexico 19-27%; Brazil 15-17%	Peru 49.3%; Mexico 57%; Brazil 23-28%	Peru 16.2%; Mexico 8%; Brazil 9-15%
Increased risk	Premenopausal, alcohol consumption, family history of breast or ovarian cancer, obesity (possibly)	Obesity, nulliparity	< 50 years
Histology	Poorly differentiated tumors	Well differentiated tumors	Poorly differentiated tumors
Protective factors	None reported	Parity, lactation	None reported
Molecular abnormalities associated	Mutations in the BRCA1 gene; Is a heterogeneous group	Drive by endocrine signaling	HER2 amplification
Response to chemotherapy	High rates of complete response	Low rates of complete response	Response to anthracycline-based chemotherapy
Prognosis	Unfavorable; favorable when complete response is achieved	Favorable	Favorable with anti-HER2 targeted therapy

With mean age at diagnosis and death of 54.0 and 58.4 years, respectively, it is estimated that breast cancer represent to Peru an annual loss of 26,644 disability-adjusted life years[11]. Peru has a high frequency of breast cancer in young women, where 42% of cases are premenopausal ≥ 35 years, 8.2% are premenopausal < 35 years, and 51% are postmenopausal women. Epidemiological data of IREN Norte (a cancer hospital located in Trujillo, in the north of Peru) shows a distribution of ages of 1.1% for women aged 20-29 years, 10.6% between 30-39 years, and 26% for women between 40-49 years[12,13].

TRIPLE-NEGATIVE BREAST CANCER EPIDEMIOLOGY IN PERU AND LATIN AMERICA

There are several reports describing the influence of racial/ethnic aspects in the prevalence of triple-negative subtype, accounting for about 21% of all breast cancers in African Americans, and 9-15% of all breast cancers in Caucasian populations[3].

A high incidence of TNBC has been also described in Latin American women, with a frequency of 24.6% in Venezuela, 23.1% in Mexico, and 27% in Brazil[14-16] (Table 1). Vallejos, et al. (2010), in a study of patients from the Instituto Nacional de Enfermedades Neoplasicas (INEN), described that 21.3% of all cases of breast cancer in Peru are TNBC, with a similar frequency to that reported by Alarcon-Rozas, et al. (2011) in a study of 1,042 patients treated in the Peruvian Social Security, where a frequency of 20.6% was described[17,18]. Other reports in patients attended in hospitals outside of Lima describe a higher frequency of this subtype of tumors. A study with a relatively small number of patients (n = 75) in Arequipa (at the south of Peru) described a frequency of 30.8%; while another study in a hospital of Chiclayo (at the north), evaluating 117 patients, reported a TNBC frequency of 32.5%[19,20].

Additionally, there is a report describing that 11.1% of the cases of breast cancer in Peruvian men correspond to the triple-negative phenotype[21].

MOLECULAR EPIDEMIOLOGY OF TRIPLE-NEGATIVE BREAST CANCER

Thanks to collaborative projects with Vanderbilt University and the MD Anderson Cancer Center, Peruvian research groups have profiled several molecular characteristics of TNBC in Peruvian patients. With regards to the frequency of PIK3CA gene mutations, they are present in 9.6% of patients and correspond to E545K (1.4%), E545Q (1.4%), H1047R (5.5%), and H1047L (1.4%)[22]. A mutational analysis using next-generation sequencing showed that there is a frequency of 89% of TP53 mutations, 54% of MCL1, 35% of MYC, 11% in BRCA1, and mutations in CDKN2A, NF1, KRAS, CCND1, AKT3, EGFR, CCND2, CCND3, IGF1R, CDK6 and CCNE1 were found in < 10% of cases[23]. Amplification of JAK2 was found in 10.2% of patients[24].

Triple-negative breast cancers showed high glycolytic activity and higher levels of LDHB gene expression[25].

Although TNBC lacks major therapeutic targets (hormonal receptors and HER2 receptor), molecular studies have determined that less than 90% of cases have mutations that could be treatable. The following pathways can be used to target directed therapy[23]:

– PI3K/mTOR pathway

– Cellular cycle

– DNA repair

– Ras/MAPK pathway

– Growth factor receptors

As we can see, Peruvian oncology has made an important contribution to the knowledge of the biology of triple-negative tumors; however, we still need to know what is the distribution of the six TNBC molecular subtypes in our population.

CLINICOPATHOLOGICAL FEATURES DESCRIBED IN PERU

It has been reported that the median age at presentation of TNBC in Peru is 48 years, with 53% of cases diagnosed before 50 years and with an average tumor size of 36 mm, where 36.4% of cases had tumors T3, 38.6% T4, and 55% had axillary involvement[26,27]. The frequency of advanced stages is 42% with five-year survival for all clinical stages of 67.1%[17,27]. The most frequent sites of recurrence are viscera (37.5%), bone (25%), skin (20%), central nervous system (12.5%), and contralateral breast (5%)[18].

SURGERY AND SYSTEMIC TREATMENT OF TRIPLE-NEGATIVE BREAST CANCER IN PERU

Surgery as initial therapy

In early breast cancer, the expression of hormone receptors and HER2 are not independent prognostic factors, as shown by Carrasco, et al. (2013). In breast cancer in stages I-III, with surgery as initial therapy, TNBC has a 2.26% five-year rate of local recurrence with a five-year rate of distant recurrence of 20.36%. In the multivariate analysis, TNBC patients have an increased risk (HR: 1.72) to develop distant metastases compared to luminal A tumors[28,29].

Systemic treatment

Agents available for the treatment of TNBC include chemotherapeutic agents such as anthracyclines, taxanes, ixabepilone, platinum salts, and antiangiogenic agents. A report of institutional experiences about response rates to chemotherapy in

TNBC reported a complete response rate of 9%, a 48.3% partial response, 1.1% stable disease, and 38.2% disease progression during the neoadjuvant chemotherapy[30]. These rates are lower compared to those described in ongoing studies which reported response rates of 20-30%[31].

ROLE OF RADIOTHERAPY IN TRIPLE-NEGATIVE BREAST CANCER TREATMENT

The use of radiotherapy for locoregional disease control in a heterogeneous neoplasm such as breast cancer is a constant challenge for everyone involved in the treatment of this disease. With historical reports of 21.9% survival in patients with locally advanced disease treated with only radiotherapy in Peru, the inclusion of the combined management and the treatment with 3D radiation therapy has improved the prognosis and reduced collateral damage[32]. An increased risk of recurrence has been described in patients with locoregional TNBC compared to other subtypes[33,34]. Abdulkarim, et al. (2011) reported locoregional recurrence rates of 10% in patients with TNBC T1-2N0, with a median follow-up of 7.2 years, in a study in breast-conserving surgery; treatment without radiotherapy was the only independent prognostic factor associated with an increased risk of locoregional recurrence[35]. The use of accelerated partial breast irradiation has shown similar results to those obtained in the treatment of hormone receptor-positive cases. In a study in 202 patients (182 positive hormone receptors and 20 TNBC), stages I-II, with unicentric tumors ≤ 3 cm, where patients had a median follow-up of 4.1 years, no locoregional recurrences events or distant metastases were observed in the group of TNBC patients[36].

CONCLUSIONS

We have similar frequencies of TNBC to those reported for other Hispanic populations, although some reports describe an increased frequency in the provinces outside of Lima. Although today we have much to learn about this disease, the effort of Peruvians oncologists to understand the biology, prognosis, and new treatment options in this class of tumors is remarkable. We hope that in the future it could be easier to evaluate molecular markers, including the molecular subtyping of TNBC, for a better identification of therapeutic strategies.

DECLARATION OF INTEREST

The authors declare no conflicts of interest.

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