Papillary squamous carcinoma of the cervix with metachronous clear cell renal cell carcinoma

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ABSTRACT

Multiple primary tumors can be classified as synchronous or metachronous. Cases have been reported, with a prevalence, in gynecologic malignancies, of 1.9 to 4.3%, and commonly occurring in endometrial and ovarian malignancies. Renal tumors coexisting with primary cervical cancer are mostly metastatic tumors, and at present, no case of cervical carcinoma metachronous with renal cell carcinoma has been reported on literature. This is a case of Papillary Squamous Cell Carcinoma of the cervix who developed a metachronous Clear Cell Renal Cell Carcinoma. Several months after the diagnosis of cervical cancer, she presented with an abdominal mass and signs of uremia secondary to obstructive uropathy. She underwent radical nephrectomy with contralateral percutaneous nephrostomy. Definitive plan for the cervical mass is concurrent chemotherapy and radiation, depending on the improvement in renal function. Currently, there are no clearly established guidelines in managing metachronous cervical and renal masses, and this presents a unique opportunity to document this case, and study its implications on management and prognosis.

Keywords: metachronous, multiple primary tumors

INTRODUCTION

Multiple primary malignancies have been reported since the early 1900s, and have a prevalence of 2-17%, depending on the study type and population ethnicity[1]. It was first described by Warren and Gates in 1932, where they described the condition as tumors occurring in different organs, with each having distinct histopathologic diagnosis, and neither is the recurrence or metastasis of the other. Multiple primary tumors can be classified as synchronous if the duration of the diagnosis is within 6 months, or metachronous if more than 6 months. Its prevalence in gynecologic malignancies is 1.9 to 4.3%, commonly occurring in endometrial and ovarian malignancies[2]. Local data is currently lacking for multiple primary malignant tumors in general, but the data from the International Agency for Research on Cancer have revealed an estimated incidence of 0.4% to 8%[1,3] Multiple primary malignant tumors have been increasing in incidence in the last few decades, due to better screening techniques, superior diagnostic modalities, and improved treatment methods.

Females in general, and those with breast cancer, have the greatest risk for developing multiple malignant tumors[1,3,4]. According to Huang et al. in 2007, only sporadic cases of renal cell carcinoma occurring with primary gynecologic cancers have been identified, and the most common co-existing tumor were ovarian and endometrial cancers. Jareemit et al. in 2018 also agreed and mentioned that the majority of non-gynecologic cancers co-existing with gynecologic cancers are metachronous, with breast cancer as the most common non-gynecologic cancer, and endometrial and ovarian cancers as the common gynecologic cancers.

Reported cases of renal tumors occurring with primary cervical cancer are mostly metastatic tumors. Renal metastases are rare and those of cervical origin are even rarer. In an autopsy series done by Zhou et al. in 2016, they noted that only 2.5% of cancers metastasize to the kidney[5]. To date, no case of cervical carcinoma metachronous with renal cell carcinoma has been reported on literature.

CASE PROTOCOL

This is a case of a 59-year-old, Gravida 3 Para 3 (3003), from Lucena City who consulted for a two-year history of postmenopausal bleeding. She is a known hypertensive, maintained on Losartan and Amlodipine and with good blood pressure control. She has no history of heredofamilial diseases. She is an elementary graduate and a 5 pack-year smoker. She had her first coitus at age 16 with 2 monogamous sexual partners. She had her menarche at age 12, occurring at regular intervals and was menopause by age 51.

She presented with vaginal spotting 6 years after menopause. Initial consult at a tertiary hospital revealed a cervical mass with a consideration of malignancy. She was

diagnosed with cervical cancer stage IIB and was referred to our institution for further management.

She is obese, with a body mass index of 29.6 kg/m2, and systemic physical examination findings were normal. On pelvic examination, she had normal external genitalia, cervix was converted to a 4.0 x 4.0 cm exophytic mass extending to the upper third of vagina, corpus was small, no adnexal masses or tenderness noted and bilateral parametria were smooth and pliable. Punch biopsy revealed Papillary Squamous Cell Carcinoma. Transvaginal ultrasound showed a cervical mass measuring 3.4 x 3.8 x 3.2 cm, consistent with malignancy, with full stromal invasion and extension to the upper third of vagina and bilateral parametria (Figure 1). Chest radiography and whole abdomen ultrasound showed unremarkable findings. She was diagnosed with Papillary Squamous Cell Carcinoma, cervix, stage IIB and was advised to undergo concurrent chemotherapy and radiation (Figure 2). However, she was lost to follow-up.

In the interim, she had intermittent vaginal bleeding, abdominal pain and difficulty in urinating. She consulted another tertiary hospital and on examination, there was note of a palpable mass at her left flank. Ultrasound showed a large rounded heterogeneous solid mass at the middle pole cortex of the left kidney measuring 11.0 x 8.7 x 10.2 cm. There was bilateral pelvocaliectasia and the right kidney and other abdominal organs were unremarkable. Ultrasonographic impression was solid left renal cortical mass, consider primary versus metastatic tumor. She remained symptomatic and due to increasing severity of abdominal pain and decrease urine output, she opted to consult again, 7 months after, at our institution and was subsequently admitted.

During her admission, there was note of a 4.0 x 4.0 cm firm mass palpated below the 12th left rib. On pelvic examination, she had normal external genitalia, cervix was converted to a 7.0 x 6.0 cm exophytic mass extending to the middle third of the vagina anteriorly and upper third of the vagina posteriorly, corpus was small, right parametrium was nodular and fixed, and left parametrium was nodular with a 0.5 cm clearance.

Transvaginal ultrasound showed intact urethra, urinary bladder mucosa and rectum. There was a cervical mass, consistent with malignancy, measuring 6.6 x 5.8 x 5.8 cm with full stromal invasion and extension to upper 3rd of the vagina, bilateral lateral parametria, and uterine isthmus. The mass had moderate central flow and low resistance indices on color flow mapping. There were multiple retroperitoneal hypoechoic masses seen at the para-aortic area ranging from 0.8 to 1.5 cm but no nodes seen along the iliac vessels. The left kidney measured 10.7 x 8.6 x 8.8 cm, with note of an irregular heterogeneous mass measuring 9.1 x 8.7

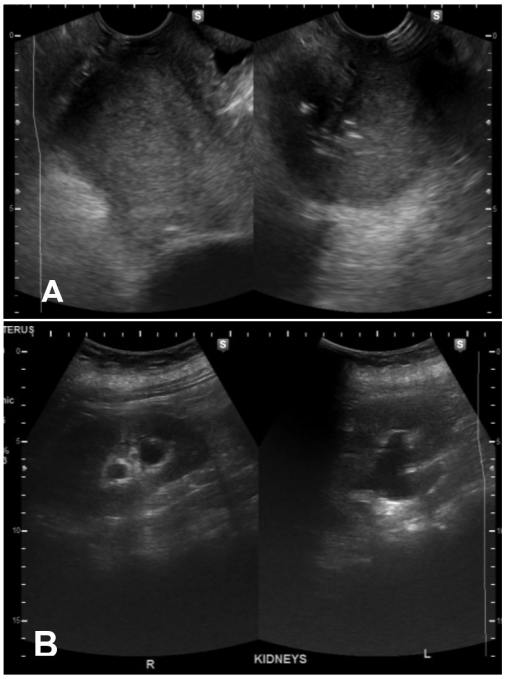

Figure 1. A. Transvaginal ultrasound sowing the cervical mass. B. Transabdominal ultrasound showing normal bilateral kidneys.

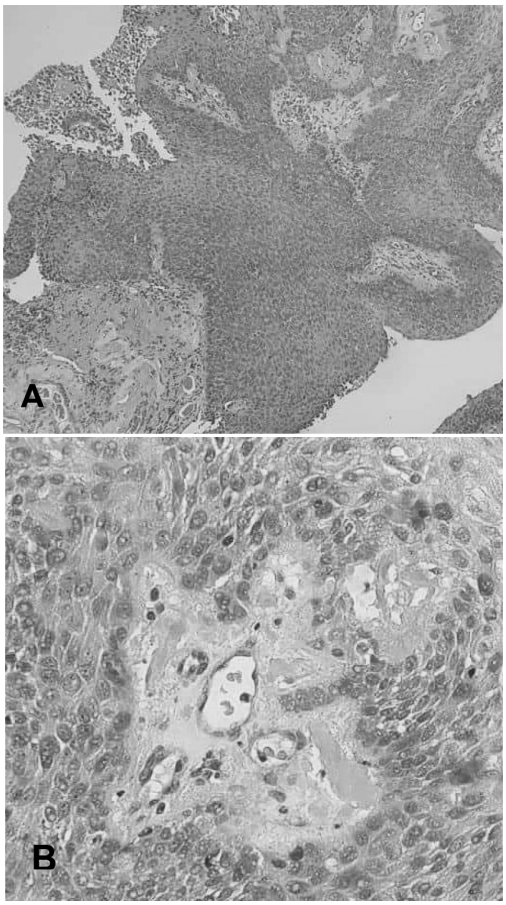

Figure 2. A. Low Power Objective (100x magnification) of Papillary Squamous Cell Carcinoma with tumor cells arranged in nests and papillary configuration. B. High Power Objective (400x). These tumor cells exhibit moderate pleomorphism, with enlarged, round to oval, nuclei, some with prominent nucleoli, and abundant eosinophilic cytoplasm and distinct cell borders.

x 6.2 cm, and with minimally dilated calyces (Figure 3). The renal capsule was smooth and intact. The right renal calyces were mildly dilated. The liver parenchyma was homogenous. She was uremic from obstructive uropathy, with an increasing trend of creatinine from 365mg/dL to 1082 mg/dL, in the span of 3 days. She underwent 5 cycles of hemodialysis and eventually underwent left radical nephrectomy with right percutaneous nephrostomy. Intraoperatively, the left kidney was converted to a 12.0 x 10.0 x 5.0 cm solid, necrotic mass with intact renal capsule (Figure 4). Histopathologic examination showed Clear Cell Renal Cell Carcinoma WHO and International Society of Urologic Pathologists grade 1, unifocal, and 8 centimeters in greatest tumor dimension (Figure 5). There was no definite lymphovascular space and perineural invasion. There was no tumor extension into the perinephric tissue, pelvocalyceal system and major vein.

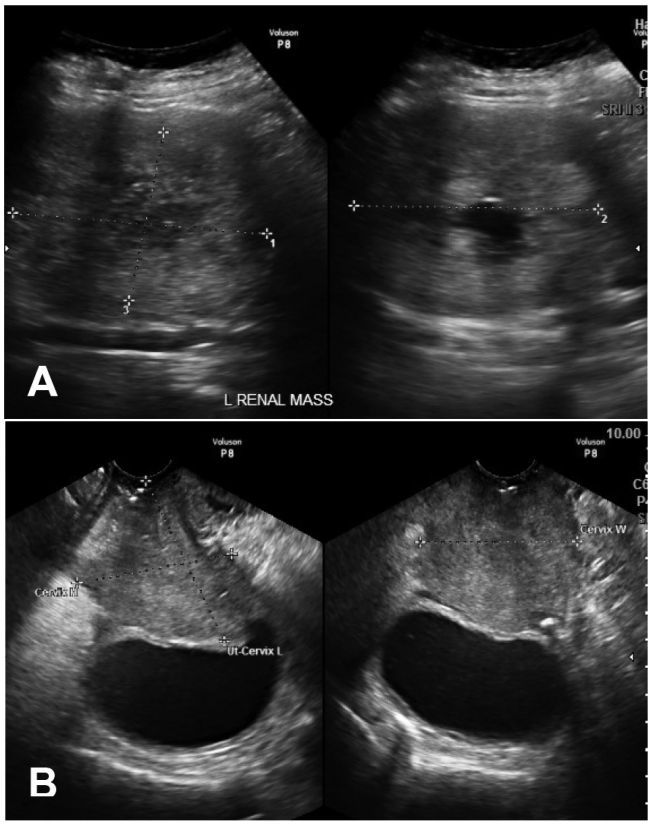

Figure 3. A. Transvaginal ultrasound sowing the cervical mass. **B.** Transabdominal ultrasound showing the left renal mass.

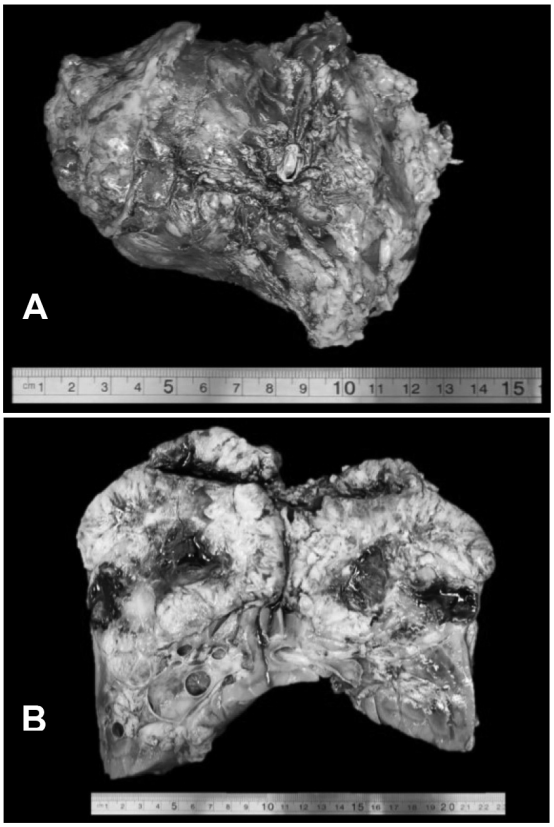

Figure 4. Intraoperative pictures. **A.** The left kidney was converted to a solid, necrotic mass measuring 12.0 x 10.0 x 5.0 cm. **B.** Cut section of the resected left kidney.

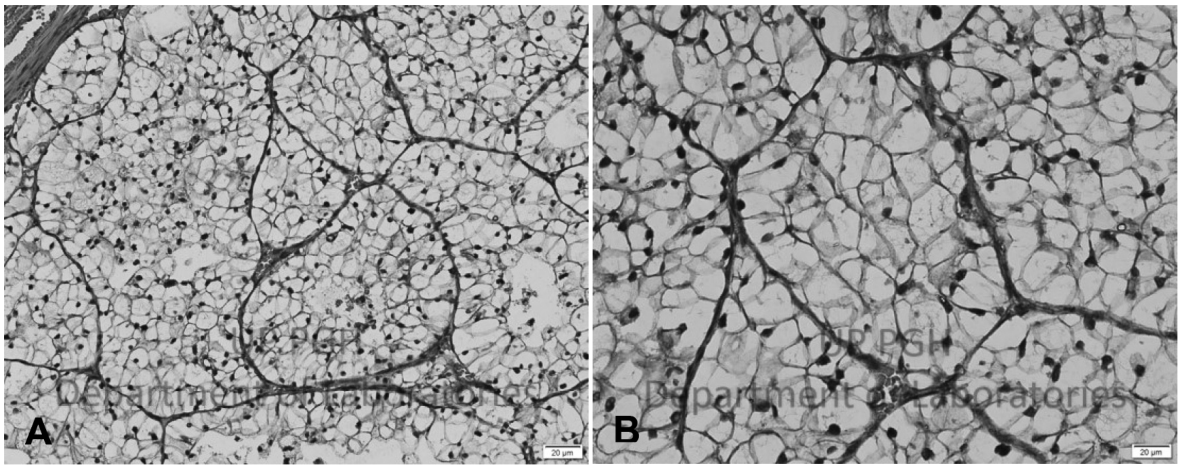

Figure 5. A. Low Power Objective (100x magnification) of Clear Cell Renal Cell Carcinoma, ISUP Grade 1, with tumor cells distributed in alveolar pattern, separated by thin blood vessels. **B.** High Power Objective (400x). These tumor cells exhibit moderate pleomorphism, with hyperchromatic nuclei, rare nucleoli, and clear cytoplasm.

DISCUSSION

The patient has Papillary Squamous Cell Carcinoma of the cervix, stage IIIB with metachronous Clear Cell Renal Cell Carcinoma of the left kidney, stage II. The renal mass was detected more than 6 months from her initial diagnosis of cervical cancer. Although renal tumors in patients often present as an incidental finding of renal mass on routine imaging, this particular patient presented with decreased urine output and a palpable abdominal mass. Only about 10% of patients present with clinical symptoms of a palpable abdominal mass, flank pain or hematuria, and 60% of patients have incidental finding of renal mass on ultrasound[6].

Factors associated with developing multiple cancers are grouped into three categories: familial and other genetic susceptibility factors, common exposures, and carcinogenic effects of cancer treatment[7]. Approximately 1-2% of cancers are associated with an inherited genetic mutation, and individuals with such mutations have a higher probability of developing cancer. Common exposures include smoking, alcohol intake, dietary factors and obesity, hormonal and reproductive factors, and infection or immunosuppression. Treatment of a primary cancer with radiation or chemotherapy can damage normal cells and result increased risk of developing a subsequent cancer. Among the enumerated factors, the most likely contributors to the patient's multiple cancers are smoking, obesity, hypertension and genetic susceptibility.

Is obstructive uropathy caused by the renal or cervical mass?

Obstructive uropathy is a sign of advanced stage disease in cervical cancer, owing to parametrial involvement or presence of extrinsic ureteral obstruction by a metastatic lymph node. Urinary diversion through ureteral stenting or percutaneous nephrostomy may be done to alleviate the obstructive symptoms. Renal cell carcinoma, on the other hand, may render the kidney non-functional but will not cause obstructive uropathy. It presents with signs or symptoms resulting from metastatic disease, such as pulmonary symptoms, bone pain and adenopathy.

In the patient, the parenchyma of the left kidney has been converted to a mass, rendering it non-functional, and leaving her with a solitary functioning right kidney. Her symptoms of decreased urine output and radiologic evidence of urinary obstruction are due to right obstructive uropathy secondary to cervical malignancy. It is indicated to do the left radical nephrectomy for tumor control and the right percutaneous nephrostomy to address the patient's obstructive uropathy and correct her deranged renal functions.

What is the treatment of Papillary Squamous Carcinoma with metachronous Clear Cell Renal Cell Carcinoma?

Treatments are tailor made for double primary malignancies, depending on the more aggressive tumor, and the clinical symptoms the patient present with.

Based on the NCCN Clinical Practice Guidelines in Oncology for renal carcinoma, radical nephrectomy remains as the curative therapy of choice for stage II Clear Cell Renal Cell Carcinoma, followed by surveillance every 3-6 months for 3 years, annually until 5 years, and as clinically indicated thereafter. Adjuvant therapy has no established role in patients who have undergone surgical resection.

For Papillary Squamous Cell Carcinoma of the cervix, stage IIIB, the treatment modality is concurrent chemotherapy and radiation followed by intracavitary brachytherapy.

For the patient, no adjuvant treatment for the renal malignancy is needed and even with a solitary functioning kidney, the treatment for the her cervical malignancy remains the same. If renal function has improved after right percutaneous nephrostomy, she may still receive radiosensitizer in the form of Carboplatin (AUC 2).

What is the prognosis of the patient?

At present, no available literature has reported on the prognosis of metachronous tumors of cervical and renal cancers. For cervical cancer stage IIIB, the five-year overall survival is 34-50%. The presence of hydronephrosis and obstructive uropathy manifest a trend towards poor survival, with a two-year survival rate of 16.8%[8]. Dienstmann et al. in 2 investigated the impact of the urinary diversion in 50 patients with cervical cancer and noted that 60% had an improvement in renal function, with a median decrease in creatinine of 2.7mg/dL[9]. Despite this, Radecka et.al in 2006 observed that the median survival of patient after percutaneous nephrostomy is 255 days.

CONCLUSION

Papillary Squamous Cell Carcinoma of the Cervix with Metachronous Clear Cell Carcinoma is a rare disease entity, with unique clinical implications stemming from each of the two malignancies. While there are no clearly established factors that link the etiologies of the two together, it is possible that a multitude of different modifiable and non-modifiable risk factors have led to the development of these two malignancies. The presence of Renal Cell Carcinoma can significantly increase the risk of compromising renal function, and cause a significant impact on the treatment of cervical cancer. While there are no clearly established guidelines for the treatment of these two malignancies co-occurring together, a treatment plan should tailor the most immediate needs and pressing clinical concerns of the patient. ■

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