

# Uterine Cervical Cancer and Chronic Kidney Disease

## An association that should not be skipped

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*We present the case of a 65 year old female patient with a history of bilateral hydronephrosis (known for about 3 years) diagnosed with keratinizing squamous carcinoma and chronic kidney disease. The low adherence of the patient to the uterine cervical cancer screening program led to the diagnosis of tumor in an advanced stage. In this patient, specific urological treatment (bilateral percutaneous nephrostomy) was not associated with significant improvement in renal function, and therefore she was deemed ESRD, dialysis dependent.*

*Keywords: cervical cancer, nephrostomy, squamous carcinoma, chronic kidney disease*

Systemic factors such as hypertension, diabetes are often incriminated in renal function decline, [1]. However, in many studies the association between renal injury and urinary obstruction is well documented. In a patient with pre-existing renal impairment - CKD (eg, elderly patients with multiple comorbidities), the occurrence of an urinary obstruction leads to Acute Kidney Injury-AKI [2,3]. As for the etiology of urinary obstruction, both benign causes (congenital malformations, benign prostatic hyperplasia, urinary calculi) and malignant causes are incriminated [4]. The renal involvement secondary to the presence of a pelvic tumor is a common clinical entity. Bladder, prostate and uterine malignancies can lead to a secondary intrinsic or extrinsic obstruction of the urinary tract [5]. Bladder bilateral obstruction due to neoplasms in the genital sphere occurs in advanced stages of illness usually result in poor prognosis [6-8]. In female patients, the occurrence of genital neoplasm is commonly associated with the occurrence of renal injury through obstructive mechanisms [7]. Among these, uterine cervical cancer is a common cause of obstructive uropathy [9,10]. Tumor extension and secondary ureteral obstruction assume the involvement of broad ligaments and the parametrium. The localization of the distal portion of the ureter at the level of the connective tissue which forms the tumor parametrium and extension at this level explains the renal involvement in uterine cervical cancers. By these modifications, the affected distal portion of the ureter determines the appearance of the ureteral obstruction. However, in uterine cervical cancer patients, lymphatic invasion and the occurrence of metastatic nodules at this level may also lead to compression at the higher ureteral levels [7]. Given that the obstructive kidney disease is encountered in advanced stages of cervical cancer, the occurrence of hydronephrosis suggests a poor long-term prognosis of the

patient with a decrease in survival rate [11-13]. To improve the quality of life of these patients, specialty studies support the association of surgical treatment of obstruction to specific oncological treatment [14]. In this regard, in patients with neoplasms in the genital sphere, in the treatment of extrinsic ureteral obstruction we mention the utility of percutaneous nephrostomy in the improvement of renal function [14,15]. However, in the case of prolonged obstruction, the restoration of diuresis by relieving of the obstruction does not always result in reversibility of renal impairment [7,14].

The purpose of presenting this case is to highlight the indisputable association between advanced stage genital neoplasia and renal impairment. It is also desirable to highlight the importance of tumor size and the duration of ureteral obstruction in the likelihood of restoring renal function in patients with advanced cervical cancer.

### Experimental part

A 65-year-old female patient with a history of about 3 years of bilateral hydronephrosis grade I-II comes in our clinic for fatigue and loss of appetite. The symptoms started 2-3 weeks prior without any identified triggering factor. Also for about 1 week, the patient had associated nausea and vomiting. Physical examination revealed elevated blood pressure (BP 190 / 85mm Hg), tachycardia (HR-94 / min, regular), pale skin and sclerae. At that time lab results revealed serum creatinine of 11.7 mg/dL, urea 168.65 mg/dL, serum hemoglobin (Hb) 6.3 g/dL, normal MCV 96.4 fl, Na 133.7 mmol / L, K 6.2 mmol / L, pH 7.36, bicarbonate 23 mmol/L. Upon admission, the patient also had significant inflammatory syndrome (ESR 57mm/1h, fibrinogen 431.59mg/dL, CRP 2mg/dL) and urine samples without significant changes. The abdominal ultrasound showed hydronephrosis gr. IV on right side and gr. III on the left;

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Bladder with transsonic content, walls of normal size. In the context of persistent symptoms, lab changes resistant to conservative treatment (increasing nitrogen retention), as well as the persistence of high blood pressure, we decided to initiate hemodialysis (using right femoral vein vascular catheter) with good tolerance by the patient and without any incidents during the procedure. In the context of suspicion of an extrinsic ureteral obstruction, we decided to do a non-contrast abdominal-pelvic CT scan to elucidate de etiology of obstruction. CT findings: Cervical uterine necrosis expansive tissue with interior, air bubbles in 39/35mm, transaxial with irregular contours, spiculated, with no limits to the posterior wall of the bladder, bilateral involvement of inferior ureteral meatus holes, oncology-free lymph nodes and bilateral hydronephrosis gr. II. Due to the changes in the uterine cervix, gynecological evaluation was requested for cervical biopsy.

## Results and discussions

The histopathological exam revealed the presence of a classical invasive keratinizing squamous cell carcinoma: invasive tumor proliferation consisting of islets and polygonal epithelial cell walls, with the formation of frequent keratosis pearls, accentuated nuclear pleomorphism. Focal prominent nucleoli, rare monstrous nuclei and increased mitotic activity, with the presence of frequent atypical mitosis.

During the admission, the extrarenal clearing is maintained with a net improvement in symptomatology and a slight decrease in BUN retention.

A urological evaluation advocated for bilateral double-J stent. After this procedure the diuresis increased from 2000-3000mL / day at the time of admission, to 4000-4500mL / day. After bilateral ureteral double-J stent, the nitrate retention products remained elevated- urea-87mg / dL, creatinine -7.72mg / dL, thus the decision was made to maintain the patient in a chronic hemodialysis program. The oncological evaluation recommends combined therapy - radiotherapy and chemotherapy with subsequent evaluation for surgical treatment of the tumor.

Uterine cervical cancer is a major global health problem, representing the second or third neoplasia in women and with an increasing incidence of 0.6% per year [15]. There are large discrepancies between developed countries and those with fewer resources in terms of incidence and mortality. The essential factor is the existence of effective screening programs and the presence of an adequate infrastructure for the management of precancerous lesions. In Romania, the incidence of cervical cancer is the highest in Europe, many cases being diagnosed in advanced stages of the disease [16].

Squamous carcinoma is the most common histological type of uterine cervical cancer (80% of cases) and is subdivided into several histological subtypes, one of them being keratinizing squamous carcinoma [17-20]. Squamous carcinoma can affect also the vulva, most commonly the patients being diagnosed after the menopause with the keratinizing type [21].

The identification of cytological changes by Pap smear, as well as the presence of clinical manifestations such as abnormal vaginal bleeding (metrorrhagia after sexual intercourse or in menopausal women), the presence of vaginal discomfort or lumbar pain may raise suspicion of cervical cancer. Early diagnosis has a positive impact on patient survival and is dependent on the recognition of the first symptoms of the disease [22,23].

In the presented case, the absence of specific cervical cancer manifestations delayed the diagnosis. An additional factor in this case was the absence of screening through

periodic cytology. At the same time, the nonspecific presenting symptoms (fatigue, GI symptoms) correlate with advanced stages of illness [24,25].

At the time of admission, lab data-elevated BUN, Cr as well as significant anemia, lead to the diagnosis to renal impairment. In this regard, it is interesting to note that in this patient, despite the fact that important kidney damage is identified, the acid-base balance is within normal limits. This is contrary to specialist studies that show a close association between decline in renal function and the occurrence of metabolic acidosis [26]. However, at this stage of the investigation, renal impairment may explain the important inflammatory status identified in this patient [27]. To complete the diagnosis, performing renal ultrasound revealed the presence of significant hydronephrosis. High suspicion of an extrinsic ureteral obstruction due to lack of nephrolithiasis history, absence of colicky pain and lack of ultrasound findings suggestive of calculus was the basis for completing the imaging with a CT. Diagnosis of keratinized squamous carcinoma was made by performing a cervical biopsy.

We mention that literature studies describe renal co-involvement in the case of extensive cervical cancers at the parametrium level [7]. In the case presented, the existence of the tumor at the genital level explains the presence of bilateral hydronephrosis secondary to extrinsic ureteral obstruction. The anatomopathological description of the tumor supports the association of oncological pathology with the patient's renal impairment.

Given a slight improvement in renal function with initiation of hemodialysis sessions, it was necessary to perform specific urological treatment in order to improve the patient's evolution [7,11-13]. In this regard, the basis for the decision to perform a bilateral nephrostomy was the description in the literature of certain benefits of this procedure in order to improve the quality of life and restore the renal function of patients with cervical cancer [14]. Despite the nephrostomy mounting, the lack of improvement in BUN, Cr lead to the decision to maintain the patient in a chronic hemodialysis program.

In this particular patient, a number of factors may contribute to the deterioration of renal function. Thus, patient's age (65 years) suggests underlying functional and structural changes that define the concept of aged kidney. Taking these into account and the addition by various mechanisms of a new injury can cause acceleration of renal decline [28]. Furthermore, prior history of hydronephrosis does not exclude the possibility of chronic renal involvement due to a preexisting obstructive nephropathy. The presence of a paraneoplastic glomerular disease in patients with genital neoplasm is well described in the literature. In the development of this paraneoplastic syndrome, the membranous nephropathy is the most commonly found glomerular change [29]. Particularly for cervical cancer, the possibility of an associated membranous nephropathy is supported by many researchers [30]. In the present case, in the absence of a renal biopsy (contraindicated at the time of admission due to the stage of CKD), it is not possible to establish a definite etiological diagnosis of renal impairment. Due to the increased risk of bleeding in this patient, the procedure could complicate associated anemia [31]. At the same time, we note that, in order to improve the patient's prognosis, it was considered appropriate to carry out surgical dissection and initiation of the oncology therapy. Regardless of the patient's underlying disease, the addition of secondary obstructive component to the presence of extensive neoplastic cervical neoplasia led to decreased renal function to the point where extra-renal treatment

methods are the optimal solution for improving the patient's prognosis. At the same time, it is worth mentioning that the literature cites cervical cancers in which chronic kidney damage due to a long ureteral obstruction can lead to the irreversibility of kidney damage when nephrostomies are placed despite the restoration of diuresis [7,14]. Not knowing precisely the timeframe of evolution of secondary hydronephrosis to tumor obstruction, we cannot exclude this possible explanation for this patient becoming hemodialysis dependent.

The choice of inserting a double-J stent for the overcoming of the ureteral obstruction in our presented case was based on this type of stent's current characteristics. The silicone and hydrophilic polymers used to fabricate the stent are responsible for two of its main features: flexibility (the silicone facilitates the atraumatic insertion of the stent) and biocompatibility (low immune response). Therefore, being made of non-toxic, biocompatible, hypoallergenic materials, it represents a safe solution, regarding the patient's safety profile, which can be used for unblocking the patient's urinary pathways without any side effects. [32,33]. Nowadays a new generation of ureteral stents are developed in correlation with some factors such as: stent encrustation, ureteral mobility and the effect of ureteral intraluminal foreign-body stimuli. [34]

Given well documented close correlation between the degree of anemia and the decline of renal function, severe normocytic anemia identified in this patient was initially deemed to be secondary to chronic kidney disease [35]. However, the identification of a tumor in the uterine cervix led us to believe that the anemia may be multifactorial - the depletion of erythropoietin secretion with the progression of chronic kidney disease and the presence of carcinoma [35, 36]. Iron deficiency anemia was excluded on the basis of the patient's negative history of vaginal bleeding and also on the basis of the identification of normal iron studies and erythrocyte indices [37].

## Conclusions

In Romania, the increased incidence of cervical cancer is due to insufficient screening programs. From the histological point of view, the most common type of uterine cancer identified in over 80% of cases is squamous carcinoma, the histopathological subtype of squamous carcinoma identified in the case presented (keratinizing squamous carcinoma), further strengthening this idea.

At the same time, we mention that in the present case, based on the delay of the diagnosis of cervical cancer and the unexpected advanced stage of disease, there was no specific symptomatology (vaginal bleeding, vaginal discomfort) and the lack of regular monitoring by cytology. The irreversibility of renal impairment secondary to ureteral obstruction relief suggests either a prolonged development of the ureteral obstruction given by the cervical carcinoma, or pre-existing renal impairment with worsening kidney function due to tumor obstruction.

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Manuscript received: 23.02.2018