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EDITORIAL

Dengue: renal manifestations

Dengue: manifestaciones renales

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Introduction

Dengue disease has reached importance relevance globally as the most frequent viral infection transmitted by a mosquito bite. The vector mosquito first appeared in Africa, then disseminated together with the slave trade from the fifteenth to nineteenth centuries. Later, global trade and tourism transported the dengue virus from endemic areas to other parts of the world, affecting not only tropical countries but also some regions of Europe and North America[1].

Definition of the disease

Dengue is a vector disease that spreads through the bite of infected *Aedes* mosquitoes, mainly *Aedes aegypti*.

The infection is produced by an RNA virus of the *Flaviviridae* family, which has four different serotypes: DENV-1, DENV-2, DENV-3 and DENV-4[2]. The disease caused by any of the serotypes presents a great diversity of clinical forms, mostly asymptomatic. On other occasions, the viral infection appears as a mild flu-like syndrome (known as dengue fever [DF]), a mild condition with fever, headache, retro-orbital pain, myalgia, arthralgia, nausea and vomiting that can last a week and represents a disabling disease[3]. However, the clinical picture can be complicated with severe manifestations as organ damage, like kidney injury[2] and even death[4]. The most aggressive form of the disease are dengue hemorrhagic fever (DHF), in which characteristic symptoms of coagulopathy, increased vascular fragility, and permeability appear. Finally, a hypovolemic shock called dengue shock syndrome (DSS) can occur[3,5].

Thus, in relation to the different manifestations that may occur in the patient, currently, the WHO establishes the following classification: dengue without warning signs, dengue with warning signs and severe dengue[6].

In relation to virulence, different factors have been described, such as the genetic variability of the different strains, the sequence of infection with particular serotypes and the time interval between them, the disease being more serious the longer the interval. All related factors of both the host and the virus must be taken into account[3].

Epidemiology of the disease

Dengue is considered one of the 3 most important emerging or re-emerging viruses at a global epidemiological level and the most relevant mosquito-transmitted viral disease in humans[7]. According to Centers for Disease Control and Prevention (CDC), the 40% world population, around 3,000 millions of people, live in risk dengue areas[3], affecting more than 100 countries, especially in tropical and subtropical areas, and with annual contagion figures that are between 100 and 400 million[5]. The reported number of cases according

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to the World Health Organization (WHO) has increased from 2.4 million in 2010 to 4.2 million in 2019[4] and it is estimated that its incidence has multiplied by more than 8 in the last 20 years and by 30 in the last 50 years[5,7], this due to climatic factors, deforestation, failure of policies for the eradication of the vector, lack of resources, lack of community awareness or ineffective vaccines, among others. Thus, all these facts and figures position this disease as one of the great public health threats in the world[5]. The WHO highlights that the increase in cases has been especially relevant in the Region of the Americas, where more than 7 million dengue events were recorded by the end of April 2024, while the global figure from the previous year was 4.6 million. However, the WHO estimates that there is underdiagnosis and underreporting, because many endemic countries do not have efficient mechanisms and infrastructure for detection and reporting, and for this reason, it established a global dengue surveillance system with monthly reporting across all WHO regions, made up of 103 countries[6,8].

Regarding the global distribution of the disease, this is determined by multiple factors such as the population density of humans and mosquitoes, our previous immunity, the particular characteristics of the circulating strains and serotypes and the conditions of the vector, such as temperature and humidity conditions[9].

Furthermore, the disease is associated with significant morbidity and mortality in the affected population, a fact that results in high economic costs, especially in developing countries[7].

The most severe forms of the disease cause around 20,000 deaths a year, which represents 20% of the cases of patients who present with these complicated dengue cases[5].

In Mexico, the southern and southeastern areas of the country are endemic and epidemiological surveillance throughout the republic is in charge of the General Directorate of Epidemiology (DGE, by its acronym in Spanish). However, and despite efforts to control the disease, in our country cases have multiplied by 10 in the last 20 years, reaching more than 264,000 cases in 2019.

Furthermore, the recent outbreaks of DENV-3 and DENV-4 and the hyper-endemicity observed in distinct Mexico states have raised concerns about epidemics of dengue hemorrhagic fever and greater severity of the disease, while the vaccine only protects between 35 and 72%. depending on the serotype and causes a greater risk of complications in seronegative subjects[9]. Additionally, it should be noted that a greater affectation has been reported in the adult population in the American continent, so the disease here is generally mild, but at the same time there is a tendency to increase DHF/DSS. In contrast, childhood involvement in Asia is greater, with more cases of severe disease[3].

Characteristics of the dengue virus

Dengue virus (DENV) is an arbovirus, belonging to the *Flaviviridae* family. It is a single-stranded RNA virus of positive polarity, spherical in shape, with a lipid envelope of 40-60 nm in diameter and an isometric nucleocapsid of 25 to 30 nm.

The minimum infective dose is established at 10 to 20 copies of the virus after the bite of the female mosquito of the genus *Aedes* (*A. aeaegypti* and *A. albopictus* as the main species, with *A. albopictus* being less efficient in transmitting the infection)[10,11]. The female mosquito acts as a vector, host and reservoir, since it remains infected throughout its life (25 to 42 days depending on environmental conditions), although without developing the disease and can even transmit DENV to the next generation. through the transovarian and venereal route during reproduction. This mosquito is also known as the tiger mosquito. Humans and other primates act as hosts and reservoirs and they do develop the symptoms of the infection[10]. Humans are the main reservoir in urban areas with a tropical and subtropical climate and the monkey in its jungle cycle[11].

The feeding habits of these mosquitoes are diurnal and they present peaks of activity during the early morning and late afternoon hours[11].

The main route of transmission being vector, there are other forms of infection such as blood transfusions or organ or tissue transplants, through punctures with infected materials or splashes, and the transplacental route, especially during the last stage of pregnancy. and being frequent during childbirth in viremic women. Moreover, some studies have found the virus in breast milk and vaginal secretions and semen, but there are no conclusive data on these transmission routes, although they are not ruled out[10,11].

The previous incubation period for DENV is between 3 and 14 days. Subsequently, the viremic period lasts between 4 and 7 days, with a maximum of 12 days and corresponds to the period in which the person is infectious and can transmit the virus. This period covers a few days before the appearance of symptoms, with a predominance of febrile symptoms and until the end of it. The extrinsic incubation period, from infection of a

female mosquito to infection of a new host, ranges between 8 and 10 days[11].

Kidney damage due to viral infections

During viral infections, the kidney can be affected indirectly, through the mechanisms involved in the immune response, or directly. In tropical areas, the indirect form is the most common and the indirect form is the least common and least known, as it is located in this climate where DENV is endemic or requires an immunosuppressed patient. In the direct form, the virus can access any space in the kidney and contrary to what happens in tropical countries, this is the form that generates the most damage in these countries, mainly involving the central nervous system and the pulmonary system and with little kidney involvement[12].

Renal alterations such as kidney lesions can be the product of multiple causes, however those that are specifically produced by viruses could be due to a cytopathic effect produced by viral proteins that directly affects glomerular and tubular cells. All this action is developed thanks to the union of virus antigens with antiviral antibodies, which induces damage by inflammatory mediators[13].

According to what was reported by Picollo Oliveira J, Burdmann E. (2015), DENV, through the proinflammatory cascade it triggers, can generate hemodynamic instability since it increases vascular permeability, leading to the loss of intravascular fluid, which triggers a reduction in renal perfusion and acute tubular injuries[2].

Proteinuria is one of the most common conditions that occur during viral infection, since according to what was reported by Horvath R, *et al.* (1999) this phenomenon occurs in 74 % of cases in which it is associated with the severity of the disease[14].

The implications of the immune system in the process of development of proteinuria are well demonstrated since there is evidence of biopsies of kidney lesions in which deposits of IgG, IgM and C3 have been found at the level of the glomeruli, which has triggered hypertrophy. of mesangial cells and thickening of basement membranes[15,16].

Specific kidney effects due to dengue

DENV presents a certain cellular and tissue tropism that can determine a particular pathogenesis, although research in this sense is scarce due to the performance of few autopsies and the limitation of resources in the countries where the disease usually occurs. Some investigations show that they have found findings of the virus in different tissues, including the kidney, which were based on autopsies in young people who had suffered DSS, however in most cases they were not related to macroscopic or microscopic evidence of serious organic involvement[5].

The mechanisms of kidney injury by the dengue virus are still not very clear, but several mechanisms can be considered, as shock mechanisms from hypotension, direct injury by the virus, the immune system, rhabdomyolysis and hemodynamic fluctuation[5].

The renal manifestations include: acute renal failure, proteinuria, hematuria and glomerulonephritis have been reported[17].

In a survey in 2020, acute kidney injury was reported in 11.8 % in dengue with warning signs and 28.6 % in severe dengue[18].

Clinical manifestations and clinical management

Within the clinical management the following can be considered: suspicious cases (clinical + epidemiological criteria); probable cases (clinical + epidemiological criteria + probable laboratory results); confirmed cases (confirmation by laboratory tests)[11].

Among the epidemiological criteria are those of placing the patient during the 15 days prior to the clinical manifestations in endemic areas, with the presence of the vector or with other probable or confirmed cases[11].

The clinical criterion refers to abrupt fever with two associated signs, which may include: severe headache, skin rash, vomiting or nausea, retro-orbitrary pain, arthralgia, low back pain and myalgia. For severe cases, the symptoms are: shock with severe plasma extravasation, respiratory distress with fluid accumulation, spontaneous hemorrhage, organ failure (heart failure, liver failure, etc.) and altered consciousness[11].

The laboratory criteria for probable cases are the detection of unconfirmed IgM by neutralization and for confirmed cases: isolation of DENV or its genetic material in a clinical sample, detection of antigens, seroconversion or 4-fold increase in titers in our isolates. at an interval of 15 days and IgM confirmed by neutralization[11].

With all the wide manifestations in dengue, it remains the clinical importance to be aware of all the damage that it can be caused in the kidney, to know how to manage dengue disease, indicate fluids and avoid nephrotoxic drugs.

Conclusions

DENV is the viral disease transmitted by mosquitoes of greatest relevance to our health, affecting more than 100 countries and more than 40% of the world's population. Kidney damage due to this disease can be caused directly by the effect of the virus on the tissue and indirectly through the immune response. The direct cause is considered the main one in regions with a non-tropical climate and the indirect one in regions with a tropical climate. In either case and depending on the cellular tropism of the virus, the kidney is one of the organs that can be affected. One of the main mechanisms by which this disease generates conditions in the kidney is thanks to the triggering of the immune response, which leads to the development of the proinflammatory cascade in a severe manner. A greater number of studies are required in endemic regions, especially in tropical countries, that allow us to glimpse the different direct or indirect mechanisms by which the virus generates kidney disease.

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Conflicts of interest

None

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ORIGINAL ARTICLE

Total replacement of the bladder urothelium with autologous colon mucosa. Experimental anatomical and functional study

Sustitución total del urotelio vesical con mucosa autóloga del colon. Estudio experimental anatómico y funcional

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Abstract

Background: *Chronic inflammation and transitional cell carcinoma originate from the urothelium. While treatment may involve partial or total removal of the bladder, Hansen initially used total mucosal denudation to treat cancer, but abandoned this technique due to complications. In selected cases, bladder preservation is sought as a treatment option for cancer.* **Objective:** *To determine whether colon mucosa can be implanted in a bladder completely denuded of its native mucosa, while preserving its anatomy and function.* **Material and method:** *An experimental study was conducted on dogs to replace the bladder mucosa entirely with autologous colon mucosa. The following were analyzed before and after the procedure: clinical course, laboratory studies, radiological evaluations, cystometry, and histopathological examination of the bladder.* **Results:** *The clinical course was satisfactory. Laboratory studies, including complete blood count, urea and creatinine levels, serum electrolytes, and general urinalysis, remained within normal limits (p = 0.28-0.86). Urine culture revealed Escherichia coli in all animals postoperatively (p = 0.01). Cystography was normal. Excretory urography remained normal in 9 out of 10 kidney units. Cystometry showed normal pressure but postoperative decrease in bladder capacity, which was not statistically significant (p = 0.218). Histopathological examination revealed normal kidney structure. Macroscopically, the bladder showed successful graft implantation, while microscopic analysis confirmed the presence of normal colonic mucosa with a clear interface between the urothelium and colonic mucosa.* **Conclusions:** *Successful implantation of colon mucosa into a bladder completely denuded of urothelium was achieved, preserving the anatomy and function of the bladder, upper urinary tract, and kidneys.*

Keywords: *Bladder. Total denudation. Mucosal replacement. Autologous graft.*

Resumen

Antecedentes: *A partir del urotelio surgen inflamación crónica y cáncer de células transicionales. Su tratamiento puede llegar a extirpación parcial o total de vejiga. Para tratar cáncer, actualmente se busca preservar la vejiga en casos seleccionados. Hansen utilizó la denudación total de mucosa. Abandono la técnica por sus complicaciones.* **Objetivo:** *Conocer si la mucosa del colon puede implantarse en la vejiga totalmente denudada de mucosa, preservando su anatomía y funciones.*

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Material y método: *Estudio experimental en perros para sustituir totalmente la mucosa vesical por mucosa autóloga del colon. Analizamos antes y después del procedimiento: Evolución clínica, estudios de laboratorio, radiológicos, cistometría y estudio histopatológico de la vejiga.* **Resultados**: *Le evolución clínica fue satisfactoria. Estudios de laboratorio: biometría hemática, urea y creatinina, electrolitos séricos y general de orina se mantuvieron normales (p = 0.28-0.86). El urocultivo mostró Escherichia coli en el post operatorio de todos los animales (p = 0.01). La cistografía fue normal. La urografía excretora se mantuvo normal en 9/10 unidades renales. La Cistometría mostro presión normal y disminución de capacidad vesical en el post operatorio sin significación estadística (p = 0.218). El estudio histopatológico revelo riñones normales. La vejiga mostró macroscópicamente implantación del injerto y al estudio microscópico se apreció mucosa del colon de características normales, con clara interfase entre el urotelio y la mucosa del colon.* **Conclusiones**: *Se logro la implantación del injerto de mucosa del colon en vejiga totalmente denudada de urotelio, con preservación de la anatomía y función vesical, del tracto urinario superior y riñones.*

Palabras clave: *Vejiga. Denudación total. Sustitución de mucosa. Injerto autólogo.*

Introduction

The urinary bladder stores and empties urine while maintaining a selective barrier through coordinated interaction of the urothelium, musculature, and neurological control. The transitional epithelium, which is composed of umbrella cells covered by specialized lipids and uroplakin, stretches, and retracts[1], regulates the passage of molecules[1], and forms an interface between the blood, bladder wall, and urine.

The urothelium acts as a sensor, and its interaction with the nervous system and its influence on the muscle are essential for bladder function[1-3]. Its cells exhibit properties similar to sensory neurons[1-3]. In pathological conditions (such as mechanical or chemical damage, infections, or inflammation), disruption of the urothelium allows substances from the urine to enter the interstitium, leading to inflammation, hypersensitivity, and alteration of nerve terminals, as seen in acute cystitis, post-radiation damage, and toxic injury[1-3]. Neurourothelial dysfunction is associated with idiopathic bladder instability, post-obstruction changes, aging, and pelvic pain syndrome and contributes to interstitial cystitis[1-4].

Bladder cancer originates in the bladder urothelium, beginning with chromosomal alterations in the macroscopically healthy urothelium. This explains the recurrent and multifocal nature of this disease. Neoplastic transformation facilitates dissemination, an irreversible process that progresses at varying rates[5]. Approximately 75% of cases are initially non-muscle-invasive cancers, but 27.2% of these cases are high-grade malignant tumors and become invasive, often metastasizing to the lymph nodes or visceral organs. The 5-year survival rate in these patients ranges from 10% to 35%[5,6]. Treatment of bladder cancer sometimes requires partial or total removal of the bladder[5-7].

Given this possibility, there is a need to find alternatives to preserve the bladder while controlling the disease in its initial stages through replacement of the bladder urothelium. In 1977, Hansen reported his experience with sixteen patients with bladder papillomatosis treated with bladder stripping. However, he eventually abandoned this technique because of pronounced bladder contracture and upper urinary tract dilatation[8].

Following the concept of replacing diseased bladder mucosa, we explored the possibility of completely replacing the bladder mucosa while preserving the anatomy and functionality of the organ. This opens the door to future bladder preservation by treating pathologies that originate and persist in the urothelium, such as chronic inflammation that is difficult to manage or non-muscle-invasive, multicentric tumors, at their early stages. In this context, we leveraged advances in the application of free grafts and tissue regeneration techniques to develop healthy mucosa, free of tumoral changes, using oral mucosa grafts already employed in urethral surgery in adults[9], children[10], and hypospadias[11]. Adequate oral mucosa can be obtained by harvesting, culturing, and expanding grafts taken from the mouth[12] or by cloning to generate non-tumor cell lines[13]. With only 1 cm² of oral mucosa, sufficient tissue can be generated to cover the entire bladder within 60 days[13].

The aim of this study was to design and implement a specific technique in experimental animals to figure out whether colon mucosa can be successfully implanted in a bladder completely denuded of its native mucosa, while preserving the anatomy and function of both the bladder and upper urinary tract. The colon mucosa was chosen based on the experience whit this structure for bladder surgery[7].

Material and methods

Experimental animals

This study was conducted in accordance with Federal regulations (NOM-062) and International Standards for Biomedical Research involving animals[14]. The experiments were performed at the Surgical Research Division of the Western Biomedical Research Center, Mexican Institute of Social Security, following approval by the local ethics and research committee (Protocol No. R-2005-1305-96).

Ten mongrel dogs were selected based on animal housing standards and supervised by a veterinarian. Five dogs were used for surgical technique standardization, and the remaining five were included in the study. Variables were assessed before the procedure and 60 days post-surgery.

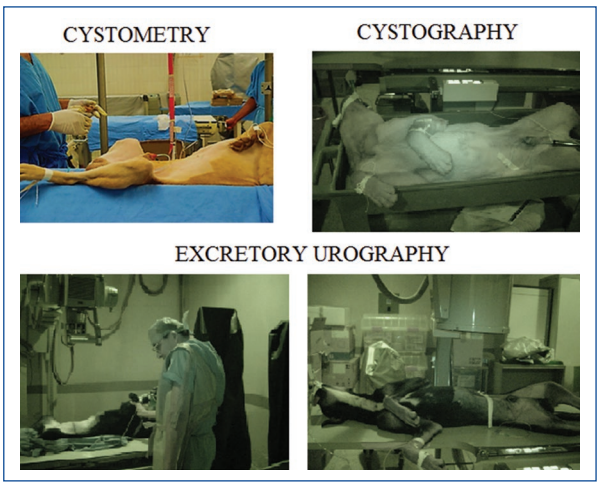

Figure 1. Cystometry and imaging procedures with animal under anesthesia.

Variables evaluated

1. Clinical evaluation – daily assessment by a veterinarian included:
   - General condition
   - Neurological, digestive, and cardiopulmonary systems
   - 24-hour urinary volume
2. Laboratory studies – Performed pre-surgery and 60 days post-surgery:
   - Complete blood count
   - Renal function (urea, BUN, creatinine)
   - Electrolytes (Na^+, K^+, Cl^-, Ca^{2+}, P, Mg^{2+})
   - Urinalysis and urine culture (>100,000 CFU/mL considered significant, Green criterion[15].
3. Office studies (Fig. 1) – Conducted before and 60 days after surgery:
   - Water cystometry
   - Cystography
   - Excretory urography
4. Morphological study – macroscopic and microscopic bladder examination.

Surgical procedure

1. Preoperative preparation
   - Oral bowel preparation: Metronidazole (35 mg/kg) and amikacin (5 mg/kg) IM every 24 h.
   - Dietary protocol: Liquid diet followed pre-surgical by a 12-hour fast.
2. Anesthetic technique & presurgical studies
   - General anesthesia: Induced with pentobarbital, fentanyl, and pancuronium[16].
   - Orotracheal intubation was performed.
   - Sample collection: blood and urine samples were taken.
   - Pre-surgical tests: cystometry, cystography, and excretory urography.
3. Surgical technique
   1. Colon Isolation (Fig. 2).
      - A midline infra- and supraumbilical incision was made.
      - A 10 cm colon segment was isolated, and end-to-end anastomosis restored colon continuity.
   2. Mucosal graft preparation
      - The isolated segment was opened along the antimesenteric border.
      - A lidocaine-saline solution (200 μg/mL) was infiltrated between mucosa and submucosa to facilitate graft separation[17].
      - The graft was immersed in lactated Ringer's solution (26°C) and shaped to fit the bladder neck and ureteral orifice (Fig. 2).
   3. Bladder modification (Fig. 3).
      - The bladder was opened anteriorly, and ureteral orifices were catheterized.
      - Lidocaine-saline infiltration aided mucosal detachment via blunt/sharp dissection.
      - Hemostasis was ensured.
   4. Graft implantation (Fig. 3).
      - The colonic mucosal autograft was secured to the bladder neck, ureteral orifices, and bladder edges using 3-0 catgut sutures.

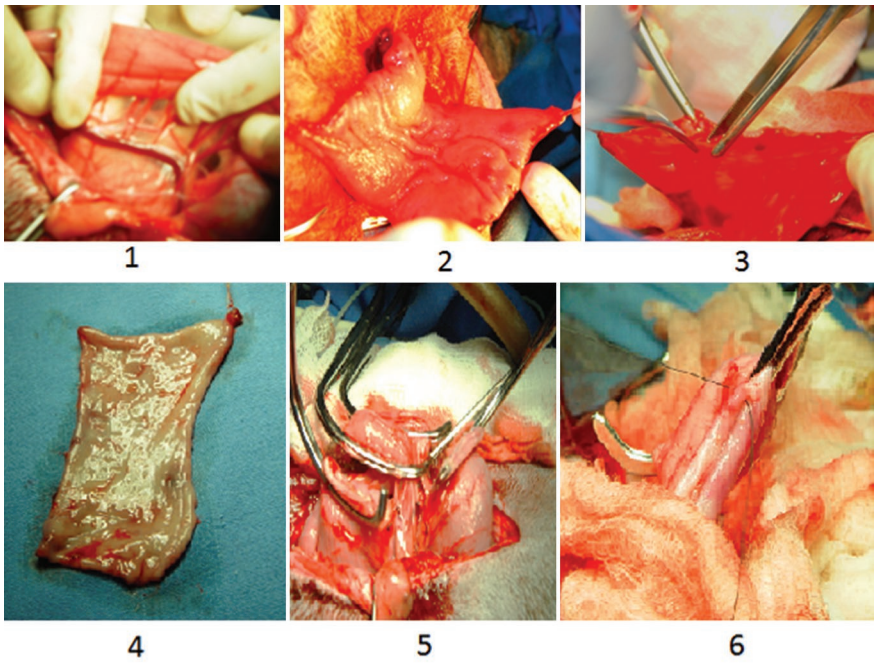

Figure 2. Procedure for taking a colon mucosa graft. **1:** colon segment selection; **2:** opening of the colon segment; **3:** removal of the color mucosa; **4:** colon mucos graft; **5** and **6:** end to end anastomosis of the colon.

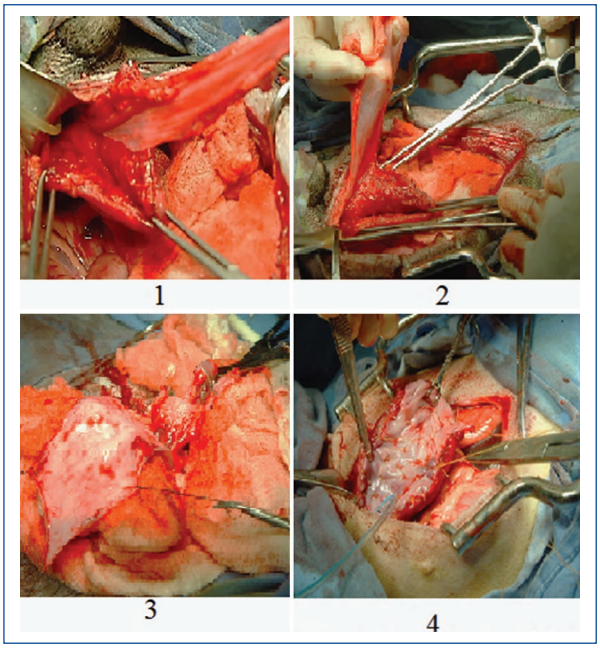

Figure 3. Procedure to remove the mucosa of the bladder and apply the colon mucosa graft. **1** and **2:** removal of the bladder mucosa; **3:** beginning of the union of the graft to the inner face of the bladder; **4:** colon graft attached to the inner surface of the bladder.

- The graft was fixed to the bladder muscular layer with interrupted sutures.
- A cystotomy tube was placed via a counter-opening, and the bladder was closed in two layers.
- A drain was left in place, and the abdominal wall was sutured in layers.
- The cystotomy tube was connected to a collection bag.
- Animals were extubated, placed in cages with Elizabethan collars, and monitored daily.

Postoperative care and euthanasia

- Diet and surveillance:
  - Wound care and general health checks were performed at least once daily.
  - A liquid diet was started 72 hours post-surgery, transitioning to a soft diet as tolerated.
- Catheter and drain removal:
  - The cystostomy catheter and Penrose drain were removed 7 days post-surgery.
  - Sutures were removed after 12 days.
- Terminal procedure (60 days post-surgery):

Table 1. Clinical evaluation and follow-up

Evaluation	General condition	Digestive system	Neurological system	Cardio-respiratory system	24-hour micturition and urinary volume
Preoperative	Normal	Normal	Normal	Normal	Normal
Immediate postoperative (1-15 days)	Satisfactory	Satisfactory	Satisfactory	Satisfactory	Satisfactory
Late postoperative (16-60 days)	Normal	Normal	Normal	Normal	Normal

- The animal was re-anesthetized, and a midline supra- and infraumbilical incision was made.
- The kidneys, ureters, and bladder were examined and excised.
- Euthanasia was performed under anesthesia via a lethal dose of potassium chloride.
- Remains were disposed of in compliance with national standards.

Statistical analysis

Data were analyzed using Chi-squared test (for categorical variables) and Student's t-test (for continuous variables). Statistical processing was performed with EPI INFO™ (v7.2.2.6).

Results

Clinical evolution: we conducted a clinical evaluation four days prior to surgery and observed that the animals were in good general condition, displaying normal attitude, behavior, feeding, urination, and defecation.

In the immediate postoperative period, we observed satisfactory progress, with no fever or complications in the digestive, cardiopulmonary, or neurological systems. Urination volume was normal, although some pain was reported during the first 4 to 5 days (Table 1).

Results of laboratory studies: laboratory studies were conducted before and 60 days after surgery. The initial blood count revealed low hemoglobin and hematocrit levels, which were corrected to the lower limit during the postoperative period. Leukocyte and platelet counts remained normal both before and after the surgery. Urea, BUN, and creatinine levels were also normal during both periods, with no significant differences observed. Electrolyte levels before and after the procedure were normal, with no significant differences.

In the urinalysis, an alkaline pH was observed before and after surgery, with preservation of urinary density and leukocyte count within normal parameters during both periods. Urine culture was negative before surgery but positive for *Escherichia coli* after surgery in all animals (Table 2).

Radiological studies: cystography and excretory urography: once dog was anesthetized in the radiography room, cystography was performed to assess the bladder and rule out vesicoureteral reflux. Subsequently, an iodinated contrast medium was administered intravenously for excretory urography.

As shown in the preoperative study, none of the five animals exhibited vesicoureteral reflux, with normal upper urinary tracts and bladders (Fig. 4). In a control study conducted 60 days after surgery, cystography revealed a normal bladder with no signs of vesicoureteral reflux. Urography showed normal renal silhouettes, calyces, renal pelvis, and ureters in four animals (Fig. 4). However, in one animal, there was grade I ectasia of the ureter and renal pelvis in the left kidney (Table 3).

Cystometry: cystometry showed comparatively lower bladder capacity after surgery, although this difference was not statistically significant ($p = 0.218$). Intravesical pressure showed no significant variation before and after the procedure (Table 4).

Histopathological study: during surgery, all bladders appeared normal, including wall thickness, elasticity, mucosal features, ureteral orifices, and bladder neck.

Macroscopic analysis of postoperative autopsies revealed that the kidneys had normal parenchymal thickness and collecting systems. The renal pelvis and ureters were normal in 9 units, while one unit showed dilation of the ureter. The bladder displayed normal muscle thickness and characteristics, and its interior was completely covered by intact mucosa, which appeared normal in color and appearance (Fig. 5).

Microscopic examination revealed the mucosa of the colon, whit crypts and bladder urothelium can be seen

Table 2. Analysis of laboratory results before and after surgery

Parameter	Preoperative: μ y σ	Postoperative: μ y σ	Difference	Value of p
Blood Cells				
Hemoglobin. N: 12-18 (g/dL)	11 ± 1.6	12.5 ± 0.96	+ 1.5	0.40
Hematocrit N: 37-55 (%)	33 ± 2.9	37.7 ± 2.4	+ 4.7	0.40
White cells. N: 6-17 (10^3/mm^3)	6.6 ± 1.9	10.6 ± 5.3	+ 4,075	0.84
Neutrophil. N: 60-77 (%)	52.8 ± 18.1	62.8 ± 3.9	+ 10.0	0.36
Platelets. N: 200-500 (10^3/m^3)	295 ± 122	225 ± 72	-70,000	0.41
Clinical Chemistry				
Urea. N: 21-60 (mG/dL)	21.4 ± 8.1	30.5 ± 8.7	+ 9.1	0.41
Urea Nitrogen (BUN). N: 10-30 (mG/dL)	9.10 ± 3.8	14.1 ± 3.97	+ 5.0	0.41
Creatinine. N: 0.5-1.5 (mG/dL)	1.04 ± 0.19	1.3 ± 0.16	+ 0.26	0.41
Serum electrolytes				
Sodium. N: 141-152 (mEq/L)	140.8 ± 7.0	144.6 ± 1.8	+ 4.2	0.28
Potassium. N: 4.37-5.35 (mEq/L)	4.3 ± 0.47	4.46 ± 0.36	+ 0.16	0.28
Chlorine. N: 105-115 (mEq/L)	112.6 ± 7.2	115.2 ± 2.7	+ 2.6	0.37
Calcium. N: 9.02-11.34 (mG/dL)	9.8 ± 0.6	10.6 ± 0.6	+ 0.8	0.41
Phosphorus. N: 2.6-6.19 (mG/dL)	6.4 ± 1.9	5.12 ± 0.4	- 1.28	0.36
Magnesium. N: 1.8-2.41 (mG/dL)	1.5 ± 0.2	1.9 ± 0.1	+ 0.4	0.26
Urinalysis				
pH. N: 5. 5-7.5 (units)	8.4 ± 0.5	8.1 ± 1.5	-0.3	0.26
Density. N: 1.001-1.070 (g/dL)	1.02 ± 0.1	1.02 ± 0.1	0	0.39
White cells. N: 0-8 (cells/field)	4 ± 3	7.8 ± 4.5	3.2	0.36
Urine Culture. N: 0 bacteria: UFC10^3/mL	Negative	*Escherichia coli*	*Escherichia coli*	0.00

N: normal values; μ = average; σ = standard deviation.

before surgery. The histological images taken after surgery show the normal structure of the kidney, including its glomeruli and tubules, as well as the bladder mucosa displaying crypt characteristics of the colon and a zone of metaplasia resembling the urothelium. The epithelial transition zone, with crypts on one side and the urothelium on the other, is visible, showing effective adaptation of the colon mucosa graft to the bladder (Fig. 6).

Discussion

Partial or total denudation of the bladder mucosa has been utilized for bladder preservation in patients with urothelial neoplasia, performed via open surgery[18-19], Neodymium YAG laser[20], or formalin application[21]. In a study by Lund et al., 10 patients with papillary neoplasia underwent bladder denudation. Among them, three experienced tumor recurrence, and one developed bladder fibrosis requiring ileocystostomy. Re -epithelialization of the bladder was observed within 5 weeks[19]. In 1968, Harada in Japan reported thirty patients with low-grade transitional cell carcinoma of the bladder treated through total mucosal denudation. No tumor recurrence was found at sites with regenerated mucosa. However, owing to complications such as severe hemorrhage, urinary extravasation, bladder contracture, vesicoureteral reflux, and hydronephrosis, the procedure was eventually discontinued[20]. Hansen et al. treated 16 patients with noninvasive bladder cancer. After 4 years of follow-up, he reported recurrence of neoplasia in 10 of the

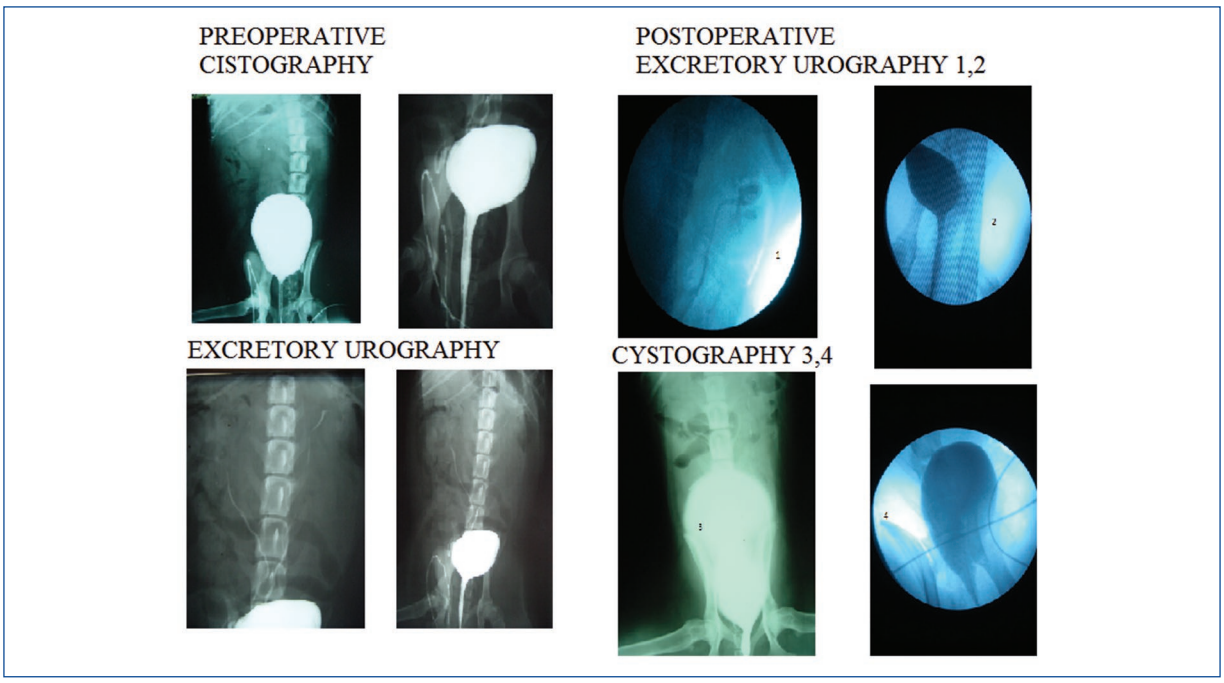

Figure 4. Imaging studies in the preoperative and postoperative period.

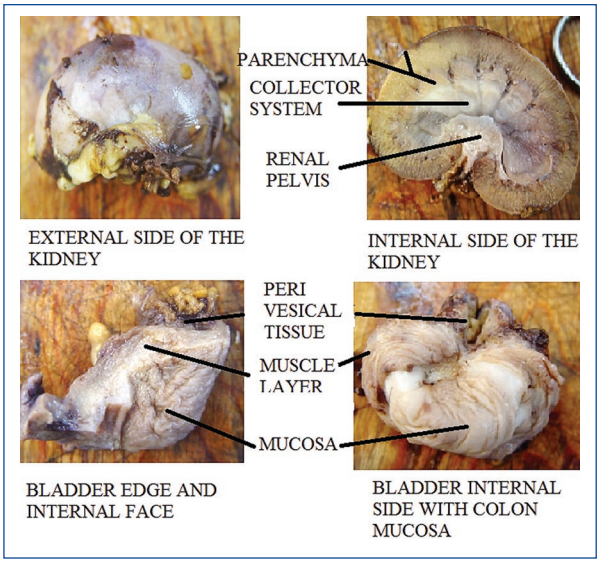

Figure 5. Macroscopic appearance of the kidney and urinary bladder after graft application.

16 patients, and half of them showed severe bladder fibrosis. Consequently, ceased recommending the procedure[8]. In 1988, Wishnow et al. reported his results using a laser for total denudation of the bladder mucosa in dogs, with complete regeneration of the bladder mucosa within 12 weeks. Radiological studies revealed a normal bladder, with no extravasation or vesicoureteral reflux. Addressing the risk of malignant cell implants in the wound during open bladder surgery, they noted that their experience with 83 patients undergoing cystotomy for the treatment of noninvasive transitional bladder carcinoma revealed no implants in the surgical wound. They also highlighted the use of external radiotherapy as a prophylaxis in selected patients[20].

Table 3. Comparative result of radiological studies before and after surgery

Parameter	Initial assessment	Final evaluation
Kidney Silhouette	normal 5/5	normal 5/5
Kidney pelvis and calyxes	normal 5/5	normal 4/5
Ureter	normal 5/5	normal 4/5
Bladder (size and girth)	normal 5/5	normal 5/5
Vesicoureteral Reflux	absent 5/5	absent 5/5

Wishnow et al. demonstrated that regeneration of the bladder urothelium occurs from the urothelium of the ureters and bladder neck, which could promote tumor recurrence if neoplasia is present in these areas[21]. A graft of mucosa foreign to the diseased urothelium can induce contact inhibition of urothelial regeneration[22], from the urethra or the ureter.

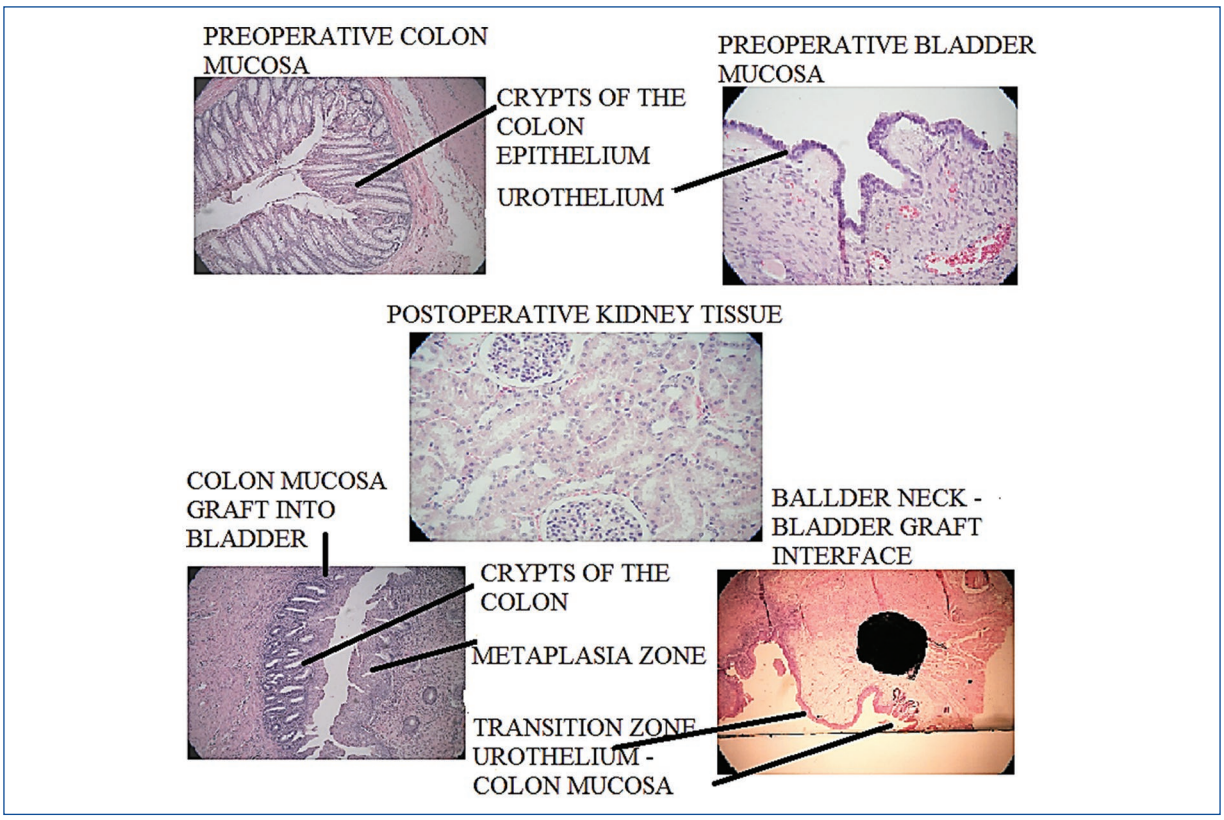

Figure 6. Microscopic appearance of the preoperative mucosa of the colon and bladder and postoperative appearance of the kidney and bladder with the colon mucosa implanted.

Table 4. Comparative analysis of cystometry results before and after the surgical procedure.

Parameter	Preoperative Mean/ Standard deviation	Postoperative Mean/ Standard deviation	P value of the difference
Bladder capacity (mL)	296 ± 100.4	200 ± 49	0.218
Bladder pressure (cm/H_2O)	14.4 ± 3.6	14.5 ± 10	0.361

Unlike earlier studies on bladder denudation, our study involved denuding the bladder and applying a colonic mucosal graft. We achieved satisfactory results, as the colon mucosa was successfully implanted, and the bladder maintained its anatomical and functional characteristics. There were no instances of vesicoureteral reflux and upper urinary tract dilation in one unit. Creatinine and electrolyte levels remained normal, and urinalysis indicated normal urine concentrations and acidification. Leukocyte counts showed no significant differences before and after surgery. Notably, all animals exhibited colonization by *Escherichia coli* in the postoperative period, which can be attributed to the nature of the graft used.

Our study supports the feasibility of total replacement of the bladder mucosa with a graft, allowing for the preservation of a functional anatomical bladder, at least in the short term. This approach could hypothetically contribute to bladder preservation strategies for treating conditions, such as urothelial cancer, which originates in the bladder mucosa. This is especially relevant given recent advances in tissue engineering, prompt diagnosis, follow-up, and treatment options—such as combined surgery (for removing diseased bladder mucosa) with chemotherapy and immunotherapy. These approaches aim at bladder preservation as alternatives to radical cystectomy[6,23,24]. This opens opportunities to develop a line of research focused on replacing diseased bladder mucosa with a buccal mucosa graft expanded in tissue culture.

The main limitation of our work is the short follow-up time.

Conclusions

We demonstrated the successful implantation of a colon mucosal graft on the internal surface of the bladder, which completely denuded of its mucosa. Our study shows that, in the short term, total removal of the bladder mucosa and its replacement with a graft are possible while preserving the anatomy and function of the bladder, upper urinary tract, and kidneys.

As a hypothesis and direction for future research, the total denudation and replacement of the bladder mucosa with a tissue culture-expanded autologous buccal mucosa graft may be a workable approach for the prompt treatment of bladder cancer, bolstered by recent advances in tissue engineering, prompt diagnosis and follow-up, and treatments aimed at bladder preservation.

We did not find any similar work reported in the literature reviewed in either English or Spanish.

Take home message

We demonstrated the successful implantation of a colon mucosal graft on the internal surface of the bladder, which completely denuded of its mucosa.

As a result, it was possible to preserve the anatomy and function of the bladder, upper urinary tract, and kidneys.

Acknowledgements

To dogs as a living reagent that must be used with justification and rationality.

Conflict of interest

None.

Funding

None.

Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely obtained and anonymized clinical data, so informed consent was not necessary. Relevant guidelines were followed.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ORIGINAL ARTICLE

Current status of urological laparoscopy in Puebla: a multicenter retrospective analysis

Estado actual de la laparoscopia urológica en Puebla: un análisis retrospectivo multicéntrico

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Abstract

Introduction: *Laparoscopy has become the standard approach in urological surgery.* **Objective:** *To describe the current status of laparoscopic urologic procedures in Puebla through a multicenter retrospective analysis.* **Methods:** *A retrospective study analyzed 492 laparoscopic urological procedures performed between 2001 and 2020. Demographics, diagnosis, surgical approach, operative time, hospital stay, and complications were reviewed.* **Results:** *71.1% of patients were male. Renal surgeries accounted for 48.5% of procedures, followed by pelvic surgeries and varicocelectomies. Operative time ranged from 60 to 420 minutes. Hospital stay ranged from 24 hours to 20 days. Trends showed improved outcomes with increased surgical experience.* **Conclusions:** *Laparoscopic urological surgery is widely practiced in Puebla with outcomes comparable to global standards. Further comparative and prospective studies are warranted.*

Keywords: *Laparoscopy. Urology. Prostatectomy. Nephrectomy. Minimally invasive surgery. Mexico.*

Resumen

Introducción: *La laparoscopía se ha consolidado como el abordaje de elección para muchos procedimientos urológicos.* **Objetivo:** *Describir el estado actual de la laparoscopía en el estado de Puebla mediante un análisis retrospectivo multicéntrico.* **Material y métodos:** *Se realizó un estudio retrospectivo multicéntrico con datos de 492 pacientes sometidos a cirugía laparoscópica urológica entre 2001 y 2020. Se analizaron datos demográficos, diagnósticos, tipo de procedimiento, tiempos quirúrgicos, estancia hospitalaria y complicaciones.* **Resultados:** *El 71.1% de los pacientes fueron hombres. El 48.5% de las cirugías correspondieron a procedimientos renales, seguidas por intervenciones pélvicas y varicocelectomías. El tiempo quirúrgico osciló entre 60 y 420 minutos. La estancia hospitalaria varió de 24 horas a 20 días. Se identificaron tendencias hacia mejores resultados con la experiencia acumulada.* **Conclusiones:** *La laparoscopía urológica en Puebla se practica de forma rutinaria con resultados comparables a los reportados en la literatura internacional. Se requiere estandarizar la formación y realizar estudios prospectivos comparativos.*

Palabras clave: *Laparoscopía. Urología. Prostatectomía. Nefrectomía. Cirugía mínimamente invasiva. México.*

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Introduction

According to the most recent census reported in 2015 by the National Institute of Statistics and Geography (INEGI), Mexico had a population of 119,938,473, with 6,183,320 inhabitants in the state of Puebla and 1,539,819 in the city of Puebla, making it the fourth most populous city in the country[1]. As for the number of practicing urologists in the city, there are more than 70 certified urologists grouped under the Puebla Urologists' College, working in both public and private institutions. Additionally, there are two residency training centers with two residents admitted per year (verbal communication from the President of the Urologists' College of Puebla). Among these practicing urologists, approximately 12 (17.1%) routinely perform laparoscopic procedures of varying complexity, including renal and prostate surgeries.

Laparoscopy was introduced in Mexico by Dr. Leopoldo Gutiérrez in 1990 with the first laparoscopic cholecystectomy[2], which soon expanded to other procedures such as fundoplication, appendectomy, and hernioplasty. In urology, Ralph Clayman reported the first laparoscopic nephrectomy in the United States in 1991, and in 1992, Schuessler performed the first laparoscopic radical prostatectomy[3]. However, both noted that these procedures were lengthy and technically challenging, discouraging their adoption at that time[4]. Nevertheless, Richard Gaston's group in France demonstrated that laparoscopic prostatectomy could be completed in under six hours[5], which led to the broader dissemination of this technique.

In Mexico, the use of laparoscopic approaches in urology was adopted later, with isolated simple cases reported as early as 1995[6]. In Puebla, the first laparoscopic procedures performed were laparoscopic varicocelectomies at the Hospital de Beneficencia Española. After 2005, urologists trained abroad through one-year fellowship programs progressively incorporated more complex procedures such as radical prostatectomy and partial nephrectomy. Simultaneously, other urologists began performing simpler laparoscopic procedures with the assistance of general surgeons trained in abdominal laparoscopy. These urologists progressively advanced from basic cases like simple renal cysts and non-functioning kidneys to more complex surgeries[7-9].

Currently, laparoscopic surgery in urology has spread worldwide, enabling most open procedures to be performed laparoscopically. Mexico is no exception. Today, laparoscopic urological procedures are routinely performed in all secondary- and tertiary-level hospitals, and some centers have even adopted robot-assisted techniques. This shift began about 15 years ago in Puebla, with teaching hospitals (such as the University Hospital of Puebla and the Mexican Social Security Institute) and private institutions incorporating this approach with resident involvement. Today, both laparoscopic and robot-assisted approaches are routinely employed.

Materials and methods

A multicenter retrospective study was conducted with data from 492 patients who underwent laparoscopic urological surgery between 2001 and 2020. Demographic data, diagnoses, type of procedure, operative times, hospital stay, and complications were analyzed. A retrospective review of medical records was performed for all laparoscopic urological procedures reported by the participating urologists in this study. Open surgeries and cases with incomplete records were excluded.

General patient data were collected, including name, age, sex, height, and weight to calculate body mass index (BMI), diagnosis, type of procedure performed, surgical diagnosis, pathology report, clinical evolution, duration of follow-up, and current status at the last consultation. Patients who did not meet these criteria were excluded. All information was entered into a database using Excel® 2013 and subsequently exported to IBM SPSS version 24 for statistical analysis and reporting.

Results

A total of 492 medical records were identified for patients who underwent laparoscopic procedures between 2001 and 2020. Of these, 142 were women and 350 were men (28.9% and 71.1%, respectively), with ages ranging from 22 to 76 years. Body mass index (BMI) ranged from 21.2 to 37, with the majority of patients presenting with grade III obesity (85.5%), followed by overweight (5.7%), normal weight (5.3%), grade I obesity (2.5%), grade II obesity (0.6%), and underweight (0.4%).

The procedures were categorized based on anatomical site: renal (including radical and partial nephrectomy, nephroureterectomy, ureteropelvic junction stenosis, renal cysts, adrenalectomy, and ureterolithotomy), pelvic (including radical prostatectomy, adenomectomy, vesicovaginal fistula repair, and partial cystectomy), and testicular (varicocelectomy), due to the high frequency of this last procedure. Nearly half of the surgeries were renal procedures (48.5%), primarily nephrectomies. The least frequently performed procedure was ureteral reimplantation (0.2%) more details are depicted in figures 1 to 4 and tables 1 and 2.

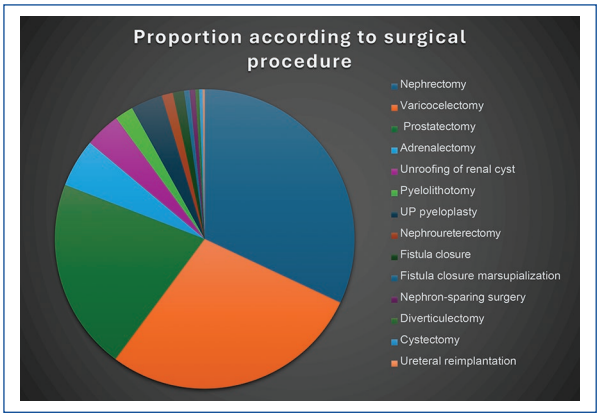

Figure 1. Distribution of surgical procedures by percentage of total reported cases.

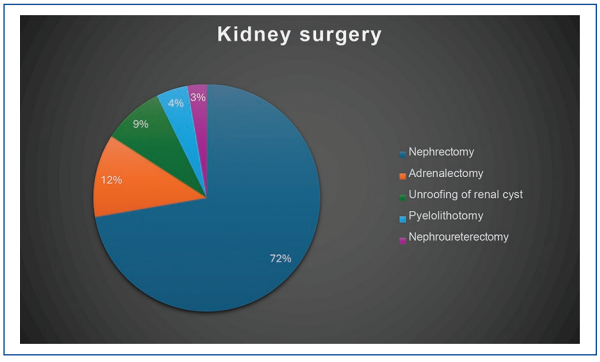

Figure 2. Percentage distribution of renal surgical procedures.

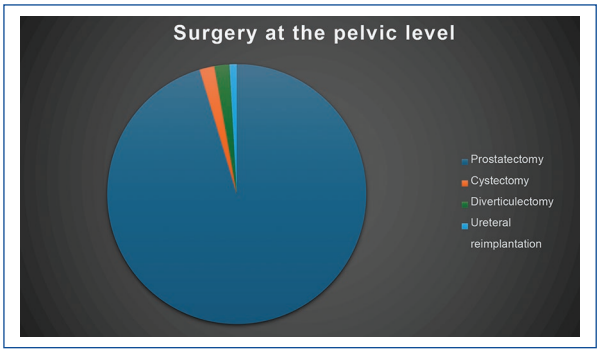

Figure 3. Percentage distribution of pelvic surgical procedures.

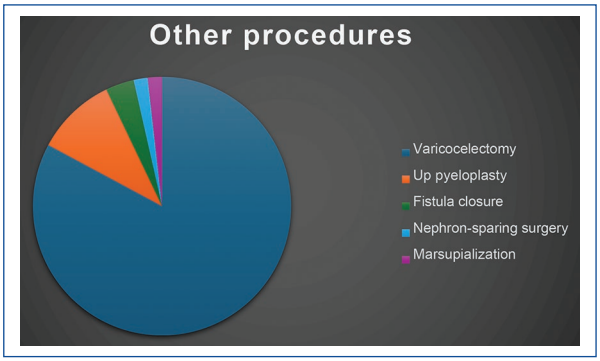

Figure 4. Percentage distribution of other surgical procedures.

Table 1. General distribution of laparoscopic procedures (n = 492)

Procedure	Frecuency	Percentage (%)
Nephrectomy (radical or partial)	184	37.4
Varicocelectomy	141	28.6
Radical prostatectomy	103	20.9
Others (fistula, cystectomy, etc.)	64	13.0

Table 2. Operative times by procedure

Procedure	Average surgical time (min)
Varicocelectomy	60-90
Nephrectomy	90-180
Radical prostatectomy	180-240
Complex cases	300-420

Operative times varied significantly, ranging from 60 to 420 minutes. The shortest procedures (90 minutes or less) were mostly nephrectomies and varicocelectomies. Medium-duration procedures (between 90 and 180 minutes) were mainly nephrectomies. Longer procedures (180 to 240 minutes) were radical prostatectomies, and the longest procedures (300 to 420 minutes) included radical prostatectomies and partial nephrectomies.

Hospital stays ranged from 24 hours to 20 days. However, hospital stay duration was not considered representative, as most patients had private health insurance and, upon request, extended their hospitalization by 48 to 72 hours for comfort or due to fear of early discharge.

Discussion

The experience gained over the years in laparoscopic surgery has enabled our urological group to

perform nearly all procedures traditionally carried out via open surgery. This progressive increase in surgical complexity has been achieved with greater safety and fewer complications, making laparoscopy the approach of choice to reduce postoperative pain and enhance recovery without compromising surgical outcomes. Although the number of cases cannot be compared to current reports from high-volume specialty centers worldwide, it has nonetheless allowed for significant progress in patient care and the publication of three original articles[10-12].

Laparoscopic approaches are now routinely used and have spread across secondary- and tertiary-level hospitals in Mexico. The wider adoption of minimally invasive techniques has been facilitated by short training programs of around three months, after which surgeons begin building their own experience in their local institutions. Due to limited infrastructure in smaller hospitals, larger institutions with extensive patient referral networks are more likely to accumulate sufficient case volumes to establish laparoscopic practice. A similar pattern has been observed in Puebla, where the number of urologists performing laparoscopic surgery has gradually increased from the original twelve.

Reported complication rates for laparoscopic radical prostatectomy in the literature range from 1.6% to 6.2% intraoperatively and from 5% to 23.7% in early postoperative periods[13]. Conversion rates during the initial learning curve vary between 1.2% and 12%[14]. Rectal injuries occur in 1-2% of cases, typically in locally advanced cancers with rectal adhesions[15], and transfusion rates range from 3% to 31%[16]. Our experience shows comparable outcomes, with a tendency toward lower complication rates as surgical experience increases—even in more complex procedures. This progressive improvement in operative time, complications, and bleeding may be attributed in part to the consistency of the surgical team, whose collective experience contributes to safer, more efficient procedures. Nevertheless, a controlled comparative study is required to confirm these findings.

We acknowledge several limitations of this study, including its retrospective nature and reliance on medical records from a limited number of public and private institutions. Many records lacked detailed surgical, complication, or follow-up data.

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. As a retrospective review of medical records without the use of personally identifiable information, informed consent and ethics committee approval were not required.

Conclusions

This study presents a collective report of laparoscopic procedures performed by urologists in Puebla—the fourth largest city in Mexico—across both private and public healthcare settings. Over time, laparoscopic approaches have been implemented for all major urological surgeries previously performed via open techniques. Our findings suggest that these procedures can be safely and effectively carried out using equipment available in most secondary- and tertiary-level hospitals in Mexico. Proper patient selection and experienced surgical teams are key to achieving complication rates, operative times, hospital stays, and blood loss comparable to those reported in the international literature. A comparative study involving other urologists in Puebla is proposed to further validate these outcomes.

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Conflicts of interest

The authors declare no financial, academic, or personal conflicts of interest related to this article.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely obtained and anonymized clinical data, so informed consent was not necessary. Relevant guidelines were followed.

Declaration on the use of artificial intelligence. The authors declare that artificial intelligence was used in the writing of this manuscript in support to writing the abstract, generating tables from the article's own information, reviewing the article, and detecting spelling errors for correction.

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ORIGINAL ARTICLE

Upper urinary tract damage in women with bladder outlet obstruction and advanced pelvic organ prolapse

Daño al tracto urinario superior en mujeres con obstrucción de la salida de la vejiga y prolapso de órganos pélvicos avanzado

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Abstract

Introduction: *Pelvic organ prolapse is a common condition in postmenopausal women. Upper urinary tract damage is an important complication of advanced genital prolapse.* **Objective:** *To determine the relationship between detrusor pressure and upper urinary tract damage.* **Material and methods:** *A cross-sectional study was performed in women with pelvic organ prolapse. Clinical and urodynamic variables were measured. Measures of central tendency, and mean difference were used to describe the population issues.* **Results:** *A total of 56 patients were studied, with grade III organ prolapse being the most frequent (73.2%). The difference in detrusor pressure between patients with and without damage to the upper urinary tract was 1.83 cmH_2O (53.58 versus 51.75 p > 0.05). The time of evolution of genital prolapse presented in the total population was 33 months. However, the average time of evolution in patients with damage to the upper urinary tract was 40 months, similar to that of the general population and the population without evident damage (p > 0.05).* **Conclusion:** *Detrusor pressure value is similar between women with and without upper urinary tract damage. Renal ultrasound may be useful in all women with advanced pelvic organ prolapse regardless of detrusor pressure in order to detect upper urinary tract damage.*

Keywords: *Pelvic organ prolapse. Urodynamics. Detrusor pressure. Renal ultrasound. Upper urinary tract damage.*

Resumen

Introducción: *El prolapso de órganos pélvicos es una afección común en mujeres posmenopáusicas. La lesión del tracto urinario superior es una complicación importante del prolapso genital avanzado.* **Objetivo:** *Determinar la relación entre la presión del detrusor y la lesión del tracto urinario superior.* **Material y métodos:** *Se realizó un estudio transversal en mujeres con prolapso de órganos pélvicos. Se midieron variables clínicas y urodinámicas. Se utilizaron medidas de tendencia central y diferencia de medias para describir los aspectos de la población.* **Resultados:** *Se estudiaron 56 pacientes, siendo el prolapso de órganos de grado III el más frecuente (73.2%). La diferencia en la presión del detrusor entre pacientes con y sin daño del tracto urinario superior fue de 1.83 cmH_2O (53.58 frente a 51.75; p > 0.05) el tiempo de evolución del prolapso genital en la población total fue de 33 meses. Sin embargo, el tiempo promedio de evolución en pacientes con daño en las*

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vías urinarias superiores fue de 40 meses, similar al de la población general y la población sin daño evidente (p > 0.05). **Conclusión:** *El valor de la presión del detrusor es similar entre mujeres con y sin daño en el tracto urinario superior. La ecografía renal puede ser útil en todas las mujeres con prolapso avanzado de órganos pélvicos, independientemente de la presión del detrusor, para detectar daño en el tracto urinario superior.*

Palabras clave: *Prolapso de órganos pélvicos. Urodinamia. Daño del tracto urinario superior. Presión del detrusor. Ecografía renal.*

Introduction

Pelvic organ prolapse (POP) or genital prolapse is defined as the descent of one or more components of the vagina (anterior and posterior wall), the uterus (cervix) or the apex of the vagina (vaginal vault in patients with a history of hysterectomy)[1].

There are few studies on the natural history of pelvic organ prolapse. One study monitored women with symptomatic, untreated prolapse for an average of 16 months and 78% had no change. The incidence of surgery for prolapse is 1.5-1.8 surgeries per 1000 women-years. Approximately 300,000 surgeries for prolapse are performed each year in the United States[2].

Risk factors for developing symptomatic pelvic organ prolapse include parity, history of vaginal delivery, age, obesity, connective tissue disorders, menopause and chronic constipation[2].

Pelvic organ prolapse should be evaluated using the POP-Q system (Pelvic Organ Prolapse Quantification System), recommended by the American Urogynecological Society (AUGS), the Society of Gynecological Surgeons (SGS) and the International Continence Society (ICS) in 1996. This measurement system consists of the evaluation of nine points corresponding to different anatomical structures, the reference for determining the degree of prolapse being the hymen, which represents the zero level[3].

The points Aa, Ba, C, Ap, Bp and D are dynamic, i.e., they are examined during the Valsalva maneuver, while the points genital hiatus (gh), perineum body (pb) and total length vagina are static (tlv), are examined during rest and are represented on a grid[2,4].

Pelvic organ prolapse can cause pelvic pressure, bulging and symptoms of bladder emptying dysfunction due to bladder outflow obstruction. Hydronephrosis may occur in about 30.6% of cases and is one of the most serious complications since it can lead to chronic renal disease[5,6].

Bladder outlet obstruction is a highly prevalent cause of lower urinary tract symptoms in men, for whom diagnostic criteria for pressure flow and nomograms are well established. Unfortunately, this is not the case in women, where the prevalence of this condition and its clinical implications have been less well studied and documented[7].

There are several nomograms based on flow rates, flow-pressure data and fluoroscopy to predict the probability of obstruction in women. However, none of them have been universally accepted[8]. In 2017 Solomon et al.[9] developed and validated a nomogram to classify obstruction in women derived from peak flow rate (Qmax), detrusor pressure at Qmax, and radiographic evidence of obstruction. An index for female obstruction (BOOIf) was developed, which can be calculated mathematically using the formula BOOIf = Pdet.Qmax - 2.2 * Qmax, i.e., if BOOIf <0 there is <10% probability of obstruction, BOOIf >5 there is 50% probability of obstruction and if BOOIf >18 there is 90% probability of obstruction[9].

Lower urinary tract symptoms are common in women with genital prolapse, mainly in advanced grades (III and IV). The most common coexisting symptoms are bladder emptying difficulty, bladder outlet obstruction and stress urinary incontinence.

Therefore, multichannel urodynamic study can provide valuable information and should be considered in patients with pelvic organ prolapse grade III and IV, in order to rule out occult urinary incontinence and/or causes of bladder emptying dysfunction[10,11].

Pelvic organ prolapse can cause pelvic pressure, bulging and symptoms of bladder emptying dysfunction due to outlet obstruction, which can manifest as reduced flow rates and elevated postvoid residual volumes. It may also be associated with recurrent urinary tract infections and conditions that can be evaluated by renal ultrasound such as ureteral dilatation, pyelocaliceal ectasia and hydronephrosis[12].

The objective of this research was to determine the relationship between detrusor pressure and upper urinary tract damage.

Material and methods

A cross-sectional study was performed after authorization from the local Health Research and Ethics authorities (R-2024-3606-093/COFEPRIS 17 CI 09 010

024). The electronic records of the patients selected from the study universe were reviewed (ECE IMSS® version 4.2.5-HOTFIX-1).

Statistical analysis included the description of the population using measures of central tendency, frequencies, and proportions. For regression, a crude analysis was used considering a significant value if $p < 0.05$. Statistical analysis was performed with EpiInfo version 7.2 (Centers for Disease Control and Prevention, Atlanta, GA, USA), Excel® (Microsoft, Redmond, WA, USA), and Open Epi (Open-Source Epidemiologic Statistics for Public Health, Bill and Melinda Gates Foundation, Emory University, Atlanta, GA, USA).

Table 1. Clinical anthropometric values of patients with POP III-IV and bladder outlet obstruction

	Media	±SD 95%CI
Anthropometric values		
Weight (kg)	65	10.5 62.1-67.8
Size (meters)	1.52	0.7 1.3-1.7
	N (56)	**Percentage**
BMI		
Normal	15	27%
Overweight	25	45%
Obesity	16	28%

POP: pelvic organ prolapse; SD: standard deviation.

Results

A total of 56 patients were included for the study (Open Epi), of which the minimum age was 42 years, the maximum age was 84 years with an average of 65 years and 69.6% were older adults. The minimum weight was 48 kg, and the maximum weight was 102 kg with an average of 65 kg. The minimum height was 1.36 m, and the maximum height was 1.7 m with an average of 1.52 m. The minimum BMI was 22.82 kg/m^2, and the maximum was 40.34 kg/m^2 with an average of 28.11 kg/m^2.

The table 1 shows the anthropometric values. It should be noted that 73% were overweight or obese, according to the WHO BMI classification. The comorbidities presented in the patients were systemic arterial hypertension in 35 cases (62.5%) and, diabetes mellitus 2 in 22 cases (39.2%). The most frequent prolapse grade was grade III in 41 patients (73.2%), while grade IV was present in 15 patients (26.8%).

Regarding the detrusor pressure of the general population, the minimum pressure was 17 cmH_2O and the maximum was 184 cmH_2O with an average of 52.14 cmH_2O. Of the population without damage to the upper urinary tract, the minimum was 17 cmH_2O and the maximum was 115 cmH_2O with an average of 51.75 cmH_2O. However, of the patients who presented some type of damage to the upper urinary tract, the minimum pressure was 19 cmH_2O and the maximum was 184 cmH_2O with an average of 53.58 cmH_2O ($p > 0.05$).

It was observed that 12 of the patients studied (21.42%) presented some type of damage to the upper urinary tract, only 1 (1.7%) presented 2 types of damage (hydronephrosis and pyelocaliceal ectasia), pyelocaliceal ectasia was present in 11 (19.6%) patients, hydronephrosis in 2 (3.5%) and ureteral dilatation in none of the patients. Of the patients with damage to the upper urinary tract, 50% presented type 2 diabetes mellitus as a comorbid condition.

The average detrusor pressure presented in the entire population was 52.14 cmH_2O and in the population without damage to the upper urinary tract was 51.75 cmH_2O; however, the average detrusor pressure presented in patients with some type of damage to the upper urinary tract was 53.58 cmH_2O, similar to that of the general population and the population without damage as evidenced by renal ultrasound. Table 2 shows the mentioned results.

Regarding the time of evolution of pelvic organ prolapse in the general population, the minimum was 1 month, and the maximum was 123 months (10.2 years) with an average of 33 months (2.7 years). Of the population without damage to the upper urinary tract, the minimum was 1 month, and the maximum was 120 months (10 years) with an average of 31 months (2.5 years). Of the patients who presented some type of damage to the upper urinary tract, the minimum time of evolution was 6 months, and the maximum was 123 months (10.2 years) with an average of 40 months (3.3 years) ($p > 0.05$).

The evolution time of genital prolapse presented in the entire population was 33.3 months and in the population without damage to the upper urinary tract it was 31 months; however, the average evolution time in the population with damage to the upper urinary tract was 40 months, like that of the general population and the population without evident damage. Table 3 depicts details.

Discussion

In the present study, the prevalence of hydronephrosis in patients with pelvic organ prolapse was 3.5%, much lower than that reported in Dancz's study, which

Table 2. Pdet values in patients with POP III-IV and bladder outlet obstruction

	Mean	p value
Pdet In general No damage to UUT With damage to the UUT	 52.14 cmH_2O 51.75 cmH_2O 53.58 cmH_2O	 p > 0.05
Frequency of damage to the UUT	**n (56)**	**Percentage**
Damage to UUT and Pdet ≥ 52 cmH_2O	4	7%
Damage to UUT and Pdet < 52 cmH_2O	8	14%
No damage to UUT and Pdet ≥ 52 cmH_2O	18	32%
No damage to the UUT and Pdet ≤ 52 cmH_2O	26	47%
Type of damage to the UUT	**n (12)**	
Hydronephrosis and pyelocaliceal ectasia	1	1.7%
Pyelocaliceal ectasia	11	19.6%
Hydronephrosis	2	3.5%
Ureteral dilatation	0	0%

Pdet: detrusor pressure; POP: pelvic organ prolapse; UUT: upper urinary tract.

Table 3. Time of evolution of POP III-IV and damage to the upper urinary tract

	Mean	
Time of evolution In general No damage to UUT With damage to the UUT	 33 months 31 months 40 months	 p > 0.05
Frequency of damage to the UUT	**N (56)**	**Percentage**
UUT damage and ≥ 33.3 months.	5	8.9%
UUT damage and < 33.3 months.	7	12.5%
No damage to UUT and ≥ 33.3 months.	13	23.2%
No damage to UUT and < 33.3 months.	31	55.4%

POP: pelvic organ prolapse; UUT: upper urinary tract.

reported a prevalence of 30.6%[6]; however, this data is very similar to that of Sidiqque, who reported a variation of hydronephrosis between 3.5% and 30.6%[5].

In relation to BMI, 73% of the patients were reported to be overweight or obese, like the Mexican study by Miranda-Mazariegos in which 85% of patients were reported to be overweight or obese[12].

Of the total number of patients with some type of damage to the upper urinary tract, 50% had type 2 Diabetes Mellitus; however, none of these patients had hydronephrosis. This result contrasts with the Dancz study, where hydronephrosis was significantly associated with the diagnosis of diabetes mellitus (21.8% vs. 8%, p = 0.009)[6].

In relation to gynecobstetric history and association of risk factors for pelvic organ prolapse, we found 96.4% of multiparous patients, like the data obtained in the Miranda-Mazariegos study, which reported 85%[12].

Regarding detrusor pressure, so far there is no cut-off point to establish renal damage in women. There is only one study performed in 1981 by McGuire, where he reported ureteral dilatation in intravenous pyelography in 81% and vesicoureteral reflux (VUR) in 68% of children with detrusor leak point pressure (DLPP) higher than 40 cmH_2O. Since this study, more than 40 cmH_2O has been considered a risk situation for UTT in children with myelodysplasia[13]. In our study we observed patients with POP III and IV with bladder outlet obstruction with an overall average detrusor pressure of 52.14 cmH_2O, very similar to those patients who had damage as those who did not. With this it can be deduced that detrusor pressure is not a parameter to determine damage to the upper urinary tract.

Regarding the time of evolution of genital prolapse and damage to the upper urinary tract, an overall average of 33.3 months was observed, very similar to that of the patients who had damage as well as those who did not. This can be interpreted as meaning that the time of evolution of prolapse is not a parameter that is related to damage to the upper urinary tract.

As for the strengths of the study, it is noteworthy that so far no other studies are known to report these results in the Mexican population, which is a novel contribution. In addition, it will serve as a milestone for the development of subsequent studies in which the association of specific factors and the presence of damage to the upper urinary tract in patients with advanced pelvic organ prolapse will be evaluated.

Finally, the main weakness was the low external validity, since the information obtained came from a small sample of patients belonging to a single-center institution, so it cannot be considered as a representative sample of the Mexican population. Furthermore, the data were collected retrospectively and the way in which damage to the upper urinary tract was determined was

by means of an operator-dependent study, which could lead to bias in the results.

Conclusion

In this study population we found that the detrusor pressure value is similar between women with and without upper urinary tract damage. Renal ultrasound may be useful in all women with advanced pelvic organ prolapse regardless of detrusor pressure in order to detect upper urinary tract damage. The prevalence of upper urinary tract damage in patients with advanced pelvic organ prolapse is 21.4% and of hydronephrosis 3.5%, lower than that reported in the international literature. Patients with Diabetes Mellitus seem to be particularly at higher risk of upper urinary tract damage.

Conflicts of interest

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Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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REVIEW ARTICLE

Microsatellite instability in prostate cancer: a current diagnostic approach

Inestabilidad de microsatélites en cáncer de próstata: un enfoque diagnóstico actual

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Abstract

Microsatellite instability (MSI), a hallmark of DNA mismatch repair (MMR) deficiency, has become an important biomarker in cancer biology. It has been extensively studied in colorectal and endometrial cancers, MSI is less common studied, but clinically impactful in prostate cancer. Tumors with high MSI in prostate cancer often demonstrated aggressive behavior, elevated the burden in tumor mutation, and potential responsiveness to immunotherapy. Accurate MSI detection is crucial for advancing in a more personalized medicine, which in turn will guide the therapeutic decisions, and improving patient outcomes. This article makes a review of diagnostic methods for MSI in prostate cancer, including immunohistochemistry (IHC), polymerase chain reaction (PCR), and next-generation sequencing (NGS). Each one of these methods offers unique advantages, with IHC and PCR being cost-effective and suitable for routine diagnostics, while NGS provides comprehensive molecular insights at a higher cost. The integration of MSI testing into clinical practice will advance the shift towards a more precise medicine, offering hope for tailored therapies and improved prognoses in prostate cancer management.

Keywords: *Microsatellite instability. Prostate cancer. DNA mismatch repair. Immunohistochemistry. Polymerase chain reaction. Next-generation sequencing.*

Resumen

La inestabilidad de microsatélites (IMS), es una característica distintiva de la deficiencia en la reparación de errores del ADN (MMR), se ha convertido en un biomarcador importante en la biología del cáncer. Se ha estudiado ampliamente en cánceres de tipo colorrectales y de endometrio; la MSI se estudia con menos frecuencia, pero aun asi tiene un impacto clínico en el cáncer de próstata (CaP). Los tumores con MSI alto en el CaP a menudo demostraron un comportamiento agresivo, elevaron la carga de mutación tumoral y una posible capacidad de respuesta a la inmunoterapia. La detección precisa de MSI es crucial para avanzar en una medicina más personalizada, lo que a su vez guiará las decisiones terapéuticas, y esta mejorará los resultados de los pacientes. Este artículo realiza una revisión de los métodos de diagnóstico de

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MSI en el CaP, incluida la inmunohistoquímica, la reacción en cadena de la polimerasa y la secuenciación de próxima generación. La integración de las pruebas MSI en la práctica clínica impulsará el cambio hacia una medicina más precisa, ofreciendo esperanza para terapias personalizadas y mejores pronósticos en el tratamiento del CaP.

Palabras clave: *Inestabilidad de microsatélites. Cáncer de próstata. Reparación de desajustes de ADN. Inmunohistoquímica. Reacción en cadena de la polimerasa. Secuenciación de próxima generación.*

Introduction

Microsatellite Instability (MSI) refers to a genetic event that is characterized by alterations in the length of repetitive DNA sequences, known as microsatellites. These so-called microsatellites are short, tandemly repeated sequences of DNA, that are typically consisting of 1-6 nucleotide motifs, which will be scattered throughout the genome. These series of repeated DNA, thanks to their repetitive nature, are going to be prone to errors that will occur during DNA replication. Usually, the DNA mismatch repair (MMR) system will identify, and correct these errors, which in turn will preserve the genomic stability. However, when the MMR system is defective, or has an error, microsatellites will become unstable, leading to the accumulation of mutations. The last mention process is increasingly identified as a cornerstone in certain specific cancers. The MSI has been particularly well-studied in colorectal, as well as endometrial cancer. One of the primary roles that MSI has in a cancer biology will make it an important biomarker, that will have diagnostic, prognostic, and therapeutic implications[1].

Having a more specific view in the context of prostate cancer, MSI is less frequently observed than in other malignancies. However, its presence is clinically significant, as it has been associated and correlated with a more aggressive tumor, and a lot poorer patient outcomes. Studies have suggested that prostate cancers with high levels of MSI (MSI-high), will have a tendency of an elevated tumor mutational burden, a higher likelihood of generating neoantigens, which in turn will result in making them potentially responsive to immunotherapy[2]. Understanding MSI in prostate cancer is essential to improving diagnostic strategies and identifying targeted treatment options.

Diagnostic approaches to MSI in prostate cancer

The accurate identification, and location of MSI is elementary in order to be able to advance personalized medicine in prostate cancer. Detecting MSI enables medical practioners (or any one attending patients), to be able to stratify patients based on their molecular tumor profile, be a guide to the therapeutic decisions that have to be taken, and to give a deeper understanding of cancer biology. There has been several diagnostic methods that have been developed, each with distinct advantages, as well as limitations. The most commonly used techniques include immunohistochemistry (IHC), polymerase chain reaction (PCR), and next-generation sequencing (NGS).

Immunohistochemistry (IHC)

IHC is a widely used technique that detects the presence, or absence of DNA mismatch repair (MMR) proteins, such as MLH1, MSH2, MSH6, and PMS2, within tumor tissues. Loss of expression of one, or more of these proteins typically indicates MMR deficiency, which will indicate a of MSI. This method has a particular valued for its accessibility, and affordability, both of these qualities are the ones making it a practical option for routine diagnostic, in both academic and community hospital settings. Furthermore, IHC has provided results in a rapid way, and can be integrated at the same time with standard histopathological evaluations of biopsy, or resected tumor samples. However, like any other diagnostic techniques it has its own limitations. It can be said that the sensitivity of IHC decreases in cases of low-level MSI, where subtle or partial defects in MMR proteins may not be detectable. Additionally, the adequate interpretation of staining patterns will require a significant amount of expertise, as variability in staining intensity or non-specific background staining can complicate the differentiation between positive and negative results[3].

Polymerase Chain Reaction (PCR)

PCR is a targeted molecular technique, that was designed to amplify and analyze specific microsatellite *loci*. Commonly tested markers have included BAT-25, BAT-26, and mononucleotide repeats, which are highly sensitive indicators of MSI. This method evaluates alterations in the length of these repeats, which signify MSI table 1 depicts molecular technical details.

Table 1. Advantages and disadvantages of the main techniques used to identify MSI

Technique	Advantages	Disadvantages
Immunohistochemistry (IHC)	– More affordable use in routine diagnostics. – Faster results integrated with standard histopathology.	– Sensitivity will decreases in cases of low-level MSI. – Interpretation requires expertise due to variability in staining intensity.
Polymerase Chain Reaction (PCR)	– Highly sensitive for specific microsatellite *loci* – Cost-effective – More accessible thanks to standardized protocols	– Limited to predefined *loci* – Potentially will be missing MSI events elsewhere – Does not differentiate between MMR gene defects.
Next-Generation Sequencing (NGS)	– Comprehensive MSI and MMR pathway analysis. – High levels of both sensitivity and specificity.	– Requires advanced equipment – Needs trained personnel – It is a high cost, making it less accessible for routine use.

PCR is highly sensitive when assessing the *loci* included in the assay, and it is also a cost-effective option for laboratories that have limited resources. Its standardized protocols, and as well as a relatively simple ways that make the work flow can make it widely accessible for the mayor part of the population[4]. Nevertheless, on the downside PCR's straight focus on a predefined *loci* can be counted as a significant limitation, as it may fail to detect MSI events occurring at *loci* outside the markers that were targeted earlier[5]. One of the things that also should be counted on is the fact that the technique cannot differentiate between the different types of MMR gene defects. This has a limiting its utility for comprehensive molecular characterization[5].

Next-Generation Sequencing (NGS)

NGS represents the most advanced and comprehensive approach for MSI detection nowadays. Contrary to IHC and PCR, NGS has the capacity of simultaneously analyze a wide range of microsatellite *loci*, as well as identify mutations in the genes associated with the MMR pathway. This particular quality makes NGS effective in order for detecting both MSI-high, and MSI-low tumors. It will also make NGS good for providing detailed insights into the genetic landscape of prostate cancer. NGS has the virtue of been both highly sensitive and specific, offering unique accuracy in detecting MSI even in heterogeneous tumor samples. It also enables the quantification of tumor mutational burden (TMB), an important biomarker for predicting response to immunotherapy[6]. Despite its advantages that were just mention, NGS has an important number of challenges. It is resource-intensive, requiring sophisticated equipment, trained personnel, and specific infrastructure (bioinformatics) in order just to process, and interpret the large volume of data that will be generated[7]. Furthermore, the fact that is a high-cost detection method will limit its widespread use in a routine clinical practice. Although it has to be mention, that it has been increasingly adopted in research, and tertiary care settings that have the financial resources to adopt this high-end technology.

Discussion

Microsatellite instability (MSI) is a highly relevant biological marker in prostate cancer, particularly due to its association with more aggressive tumors and its potential response to immunotherapies. This feature is becoming increasingly recognized as an essential biomarker, for those looking for an in-cancer diagnosis[8]. Also helping in the subsequent management of the treatment the patient has to undertake, with its role in prostate cancer increasing gaining attention.

Accurate detection of MSI is crucial for personalizing treatments and improving patient outcomes. There are various techniques for diagnosing MSI, each with its own strengths and limitations. Immunohistochemistry (IHC) and PCR are more accessible and cost-effective methods, ideal for initial evaluations[9]. On the other hand, next-generation sequencing (NGS) offers greater precision and analytical capacity but is more expensive and complex.

Despite its lower prevalence in prostate cancer compared to other malignancies, MSI-high tumors are associated with more aggressive behavior, resulting a higher poor outcome, and a heightened likelihood of response to immunotherapy[5]. The choice of diagnostic method significantly impacts the precision and accessibility of MSI detection. The choice of diagnostic

method will depend on factors such as resource availability, case complexity, and clinical objectives. The implementation of these techniques in clinical practice will enable progress towards precision medicine and improve outcomes for patients with this type of cancer.

Each of these three methodologies has its own set of strengths, and weaknesses that in a clinical setting will determine which should be the one put in place. The Immunohistochemistry (IHC), and Polymerase Chain Reaction (PCR) have been able to remain the most practical, as well as cost-effective (cheaper) options for initial diagnostic assessments[10]. The just mention qualities have drawn attention particularly in a more resource-constrained environments. On the other hand, NGS, while in the high-end and more expensive, has provided a level of detail, and also accuracy that is critical in the settings for complex cases, and scientific research applications. The choice of a diagnostic approach will be determined by several factors, including the clinical scenario the patient presents at any given time, as well as the availability of laboratory resources, and last but not least the specific requirements of the patient or research study[11]. The implementation of these diagnostic methods requires a thin balance between their diagnostic capabilities, costs, and clinical utility. Without never loosing site that the ultimate goal, should be improving the patient outcomes through precision medicine[12].

Conclusion

Microsatellite instability in the not so far future will represent a starting point as a biomarker evolving in the way prostate cancer is management, and treated. The different diagnostic techniques will include the three main techniques: IHC, PCR, and NGS. Each one of method offers a specific advantage, being IHC and PCR the most accessible, as cost-effective, meanwhile NGS providing detail as well as accuracy.

The choice of diagnostic method should align with clinical needs, resource availability, and the complexity of the case. Usually being the resource availability the main reason, to choose that particular diagnostic method. While IHC, and PCR remain viable options for routine diagnostics (thanks to the lower cost), in the other hand NGS stands out for its higher capabilities, despite being resource-intensive. The increasing integration of MSI testing, is a highlight of a trend of a shift toward a more personalized medicine. This will enable personalize therapeutic strategies, and with the improved patient outcomes. Advancing toward a MSI diagnostics in prostate cancer will hinge a balancing technology and accessibility. This will refine existing techniques and addressing barriers to implementation, that will help treating clinicians a optimize use of MSI as a biomarker. This approach not only will aid, in understanding tumor biology but also will align with the overarching goal of improving survival probabilities and increase the quality of life for patients that have been diagnosed with prostate cancer.

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Conflicts of interest

The authors declare that there is no conflicts of interest of any kind.

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Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

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REVIEW ARTICLE

The mechanism of Bacillus Calmette-Guérin (BCG) immunotherapy for bladder cancer: a short review

El mecanismo de la inmunoterapia con Bacillus Calmette-Guérin (BCG) para el cáncer de vejiga: revisión corta

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Abstract

Bladder cancer, particularly non-muscle-invasive bladder cancer (NMIBC), is characterized by a high recurrence rate, which results in ongoing treatment and surveillance costs. This condition represents one of the most significant expenditures within the healthcare system. Various treatment modalities are available, including surgical options such as transurethral resection, as well as intravesical therapies like Bacillus Calmette-Guérin (BCG). Additional treatment approaches encompass chemotherapy, radiotherapy, and immunotherapy. The complexity and financial implications associated with managing bladder cancer necessitate a comprehensive and vigilant approach to patient care.

Keywords: *Bladder cancer. BCG. Immune activation.*

Resumen

El cáncer de vejiga, específicamente, no músculo-invasivo (CCNMI), se caracteriza por una elevada tasa de recidivas, lo que conlleva costes continuos de tratamiento y seguimiento. Esta enfermedad representa uno de los mayores gastos del sistema sanitario. Existen varias opciones de tratamiento, entre las que se incluyen opciones quirúrgicas como la resección transuretral y terapias intravesicales como el Bacilo de Calmette-Guérin (BCG). Otros enfoques terapéuticos son la quimioterapia, la radioterapia y la inmunoterapia. La complejidad y las implicaciones económicas asociadas al tratamiento del cáncer de vejiga exigen un planteamiento integral y prudente de la atención al paciente.

Palabras clave: *Cáncer de vejiga. BCG. Activación inmunitaria.*

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The mechanism of Bacillus Calmette-Guérin (BCG) immunotherapy for bladder cancer involves a complex immune activation and interaction with cancer cells. However, these cells can also develop evasion strategies that reduce treatment effectiveness BCG preferentially binds to bladder cancer cells rather than normal or healthy urothelial cells through two main mechanisms:

Immune activation and interaction with bladder cancer cells (Fig. 1)

The glycosaminoglycan (GAG) layer of normal urothelial cells has a strong negative charge that repels the cell membrane from BCG, which is also negatively charged, thus reducing its adherence to healthy cells. Conversely, tumor cells suffer injury to their GAG layer, decreasing their surface's negative charge. This reduction in negative charge decreases repulsive forces and increases BCG adhesion to cancer cells[1,2].

The second mechanism is related to the fibronectin-binding protein (FAP) expressed by BCG on its cell wall, which binds to fibronectin (F), a glycoprotein presents in the membrane of bladder cancer cells. Fibronectin acts as a bridge that binds to integrin $\alpha5\beta1$ on tumor cell membranes. This PAF-fibronectin-integrin $\alpha5\beta1$ complex promotes BCG adhesion and can be internalized by cancer cells through a caveolin-dependent pathway. This mechanism is more active in cancer cells due to increased fibronectin expression or altered integrin activity than in normal urothelial cells. This internalization induces bladder cancer cells to act as antigen-presenting cells. BCG can induce apoptosis or necrosis of bladder cancer cells through caspase- and oxidative stress-dependent pathways (e.g., nitric oxide production), contributing to tumor cell death[1-3].

BCG stimulates both innate immune cells (neutrophils, macrophages, natural killer (NK) cells, and dendritic cells) and adaptive immune cells (CD4+ and CD8+ T cells). B cells infiltrating the tumor may have a protective role; however, their precise function in immunity and therapeutic response to BCG is unclear. Cytokines such as IL-2, IL-12, IFN-γ, and TNF are crucial in driving a Th1 immune response associated with treatment success in bladder cancer[4].

BCG therapy induces the activation of adaptive immunity, characterized by increased infiltration and activation of CD4+ and CD8+ T cells, both locally and systemically. CD4+ helper 1 (Th1) T cell responses involving cytokines such as IL-2, IL-12, and interferon-gamma (IFN-γ) are essential for effective antitumor immunity[3,4].

Furthermore, BCG instillations into the bladder induce local immune responses and systemic immune activation. Several studies have shown that BCG vaccination and intravesical BCG therapy induce a phenomenon known as "trained immunity", a form of long-lasting innate immune memory in hematopoietic stem cells and multipotent progenitors in the bone marrow. This leads to epigenetic and transcriptional modifications that enhance myelopoiesis and produce monocytes and macrophages with a proinflammatory phenotype. Trained immunity is a concept where the immune system 'remembers' previous encounters with pathogens and responds more robustly to subsequent challenges, including those in the bladder tumor microenvironment. These trained innate immune cells can respond more robustly to subsequent challenges, including those in the bladder tumor microenvironment[5].

Peripheral blood mononuclear cells (PBMCs) from BCG-vaccinated individuals show increased production of cytokines such as tumor necrosis factor (TNF), interleukin-1β (IL-1β), and interleukin-6 (IL-6) after stimulation with various antigens. This increase in cytokine production reflects a trained immune phenotype and suggests systemic immune priming beyond the bladder itself[6].

Circulating innate immune cells, such as monocytes, NK cells, and neutrophils, are activated and recruited to the bladder following BCG therapy. NK cells contribute to cytotoxicity against bladder cancer cells, and neutrophils release factors such as TRAIL, which induce tumor cell apoptosis. Systemic activation of these cells strengthens local antitumor immunity[7].

BCG treatment can increase the expression of programmed death ligand 1 (PD-L1) on tumor cells inhibiting T cell-mediated cytotoxicity and contributing to immune escape. High PD-L1 expression correlates with BCG failure. BCG failure, which occurs in approximately 40% of patients, is a significant challenge in bladder cancer treatment. Persistent antigen exposure and a high tumor neoantigen load can cause CD8+ T cell exhaustion or anergy, reducing their cytotoxic function and leading to recurrence after the initial response to BCG. Recurrence is another major concern in bladder cancer treatment, highlighting the need for more effective and personalized approaches[7,8].

Regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages (TAMs) in the tumor microenvironment can suppress effective antitumor immunity, limiting the efficacy of BCG. Some bladder cancer cells can produce human β-defensin 2 (HBD-2), which inhibits BCG internalization and potentially decreases its effectiveness[8].

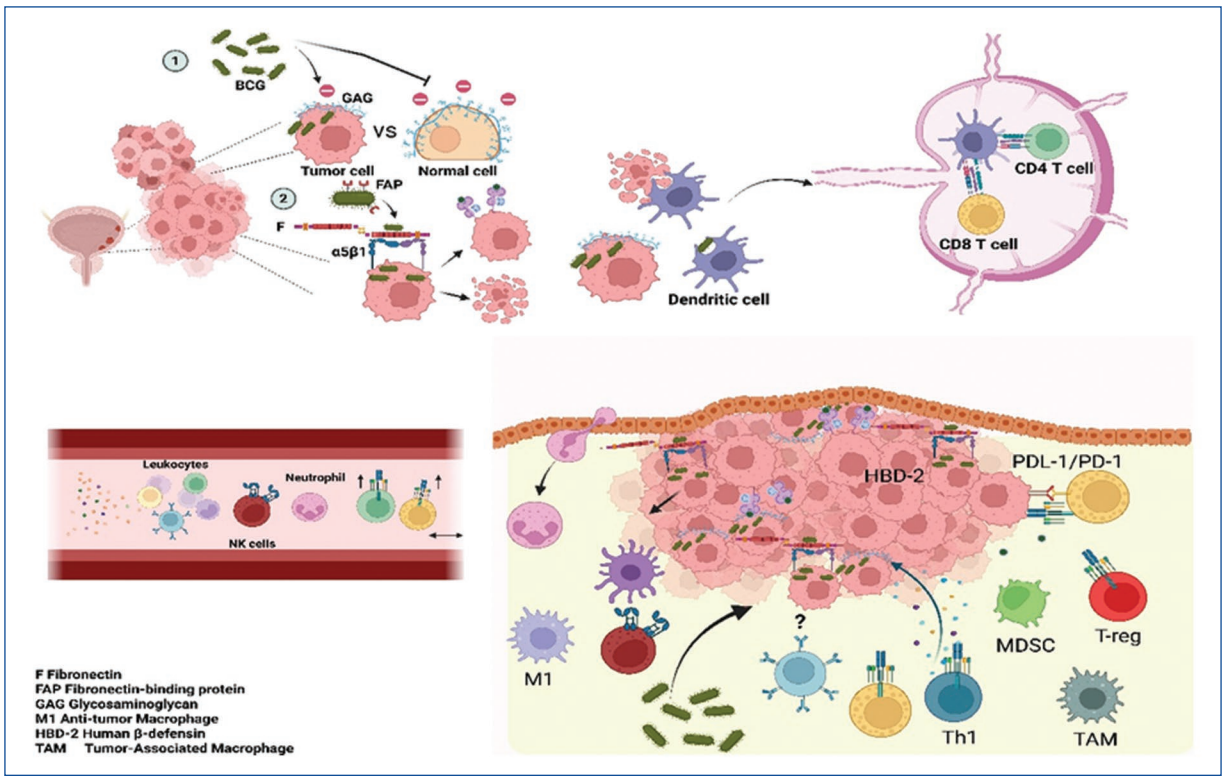

Figure 1. Immune activation and interaction with bladder cancer cells.

The future of bladder cancer immunotherapy with BCG lies in further comprehension of the mechanisms of action of this therapy to understand how BCG interacts with bladder cancer cells and the immune system. This will clarify how it induces tumor regression and controls recurrence. A detailed study of the expression pattern of activating and inhibiting receptors and immune checkpoints in innate and adaptive cells will allow us to overcome immune resistance, harness trained immunity, and personalize therapy based on tumor- and patient-specific factors. These advances offer hope for improving the efficacy and safety of BCG and expanding its clinical utility[9].

Approximately 40% of patients do not achieve satisfactory results with BCG therapy. By unraveling the complexities of the immune system, we could uncover biomarkers that predict treatment response or failure, opening the door to more personalized approaches. Notably, immune checkpoints, with PD-1 and PD-L1 as key players, exert a significant influence on the immune response. Therefore, it is essential to explore the diverse phenotypes of both immune and adaptive cells, as well as the dynamic expression patterns of activating and inhibitory receptors in response to BCG therapy for bladder cancer[1,3,9].

The success of BCG treatment hinges on the effective activation and modulation of the immune system. This exploration will deepen our understanding of the immune mechanisms at play, potentially leading to the development of enhanced BCG formulations and innovative combination therapies, such as those involving immune checkpoint inhibitors, that promise greater efficacy while minimizing adverse effects[5-8].

In summary, studying the immune response to BCG therapy for bladder cancer is fundamental to elucidating the mechanisms underlying therapeutic success and failure, improving patient selection, guiding the design of better treatments, and optimizing patient outcomes.

Conflicts of interest

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PERMANYER

CLINICAL CASE

Incidental urothelial bladder papilloma: about a case

Papiloma urotelial vesical incidental: a proposito de un caso

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Abstract

Urothelial papilloma is a rare, benign, polypoid bladder tumor covered by urothelium indistinguishable from normal urothelium. It presents in patients between 23 and 87 years of age, mainly those under 50 years of age with no history of malignancy, with a male to female ratio of 2:1. The clinical spectrum of presentation ranges from painless hematuria to asymptomatic patients, demonstrating its presence as an incidental finding. Understanding the biological character and establishing the correct differential diagnosis between the various papillary tumors is of priority importance for the treatment and prognosis of patients.

Keywords: *Papilloma. Urothelial. Bladder. Tumor.*

Resumen

El papiloma urotelial es un tumor vesical polipoide, benigno y poco común, cubierto por urotelio indistinguible del urotelio normal. Se presenta en pacientes entre los 23 a 87 años, principalmente en menores de 50 años sin antecedentes neoplásicos, con una proporción de hombres a mujeres de 2:1. El espectro clínico de presentación abarca desde la hematuria indolora hasta los pacientes asintomáticos, demostrando la presencia del mismo como un hallazgo incidental. Comprender el carácter biológico y establecer el diagnóstico diferencial correcto entre los diversos tumores papilares es de importancia prioritaria para el tratamiento y pronóstico de los pacientes.

Palabras clave: *Papiloma. Urotelial. Vejiga. Tumor.*

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Introduction

Historically, different authors, such as Mostofi, Eble, and Young, have revised and used the term bladder urothelial papilloma differently[1]. Urothelial papilloma is defined by the World Health Organization (WHO) as a rare, benign, polypoid tumor covered by urothelium indistinguishable from normal urothelium. The diagnostic criteria for urothelial papilloma were defined in the WHO/International Society of Urological Pathology (ISUP) classification system for urinary tract tumors in 1973 and were recently updated in 2022[2]. Bladder tumors are divided into: a) penetrating tumors and b) non-penetrating tumors, which include urothelial papillomas. The WHO/ISUP system further separates non-invasive papillary neoplasms into different categories that are necessary to make the differential diagnosis, as shown in table 1. Non-invasive papillary urothelial neoplasms represent 45% of all bladder tumors, of which papillomas comprise 1-4%. Urothelial papillomas can occur in 2 forms: as a primary (de novo) lesion, without a history of urothelial tumor, or as a secondary lesion, associated with previous or concurrent higher-grade tumors. Histologically, it is a small, exophytically growing lesion characterized by discrete, non-fused papillary fronds with central fibrovascular cores lined by cytologically and architecturally normal urothelium[3]. That is, a multilayered epithelium composed of basal, intermediate, and surface cells, whose thickness varies with the state of bladder distension (2-4 cell layers when dilated and 5-6 layers when contracted). It is usually solitary and has a normal number of cell layers, that is, less than 7 layers thick (normal epithelial thickness). Microscopically, the superficial "umbrella" cells are prominent, and mitotic figures are absent. Most urothelial papillomas express cytokeratin 20 (CK20) and standard isoform CD44 antibodies in a staining pattern similar to normal urothelium. The Ki-67 staining index is positive in only 4% of urothelial papilloma cells. Oncogenic mutations have been reported in FGFR3 (75% of cases), PIK3CA, KRAS, HRAS, and the TERT promoter (C228T)[4].

Table 1. WHO classification of urinary tract tumors - non-invasive urothelial tumors (5th Edition - 2022)

Urothelial carcinoma in situ
Low-grade papillary urothelial carcinoma
High-grade papillary urothelial carcinoma
Papillary urothelial neoplasm of low malignant potential
Urothelial papilloma
Inverted urothelial papilloma

WHO: World Health Organization.

Figure 1. Simple abdominopelvic tomography with hyperdense image in the proximal right ureteral tract.

Clinical case

A 51-year-old male patient with a past medical history positive for systemic hypertension, dyslipidemia, and smoking presented to the emergency department with a 48-hour history of severe, intermittent, right-sided low back pain, radiating to the ipsilateral abdomen, groin, and genitals, accompanied by frequency, tenesmus, urgency, nausea, and poor general condition. Physical examination revealed a positive right Giordano sign. Laboratory tests showed a complete blood count with leukocytosis at the expense of neutrophilia, normal nitrogen levels, and a urinalysis with uncountable red blood cells per field and calcium oxalate crystals. A simple abdominopelvic tomography (CT) was performed, revealing a hyperdense image in the proximal right ureteral tract, measuring 1.0 × 0.8 cm, with an attenuation index of up to 1320 Hounsfield units (Fig. 1), confirming the diagnosis of right ureteral lithiasis. Surgical treatment with right laser ureterolithotripsy was indicated. Incidentally, during cystoscopy, a

bladder tumor was identified in the lower left lateral wall of approximately 5 mm (Fig. 2), close to the left ureteral orifice, followed by en bloc bipolar transurethral resection of the bladder (TURBT) during the same surgical procedure. Histopathological examination of the lesion revealed fibroconnective tissue lined by mature transitional epithelium with a papillary exophytic lesion with simple branches, lined by the same type of epithelium. There were no signs of malignancy, consistent with a urothelial papilloma measuring 3 mm in major axis (Fig. 3). The patient has currently remained asymptomatic and is under close surveillance and follow-up with imaging studies and biannual follow-up urethrocystoscopies to be performed for a period of 5 years.

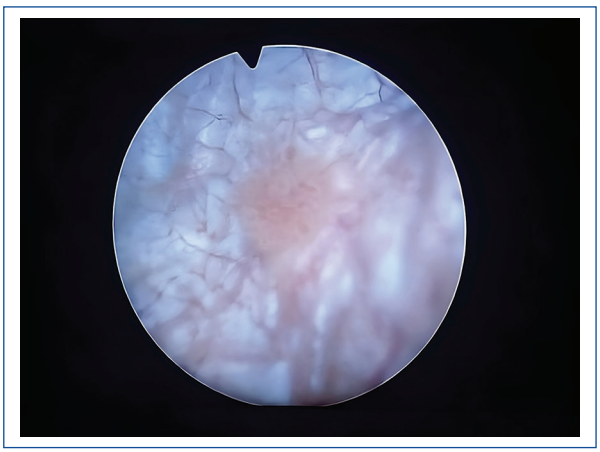

Figure 2. Papillary tumor in the lower left lateral bladder wall.

Discussion

Urothelial papilloma occurs in patients aged 23 to 87 years, primarily in patients younger than 50 years (young adults) with no history of neoplasia, with a male-to-female ratio of 2:1. It is unusual in the pediatric population but has been reported. Documented environmental risk factors include smoking and occupational exposure to aromatic amines. The clinical spectrum of presentation typically includes painless hematuria (gross or microscopic), irritative symptoms (urinary urgency and frequency), or asymptomatic patients, demonstrating its presence as an incidental finding. They are usually observed during bladder ultrasound or endoscopic treatment. Ultrasonography is the most commonly used study and allows tumors with an average size of 5-50 mm to be observed. However, lesions smaller than 5 mm cannot be detected, in which case computed tomography urography (CTU) may be preferred. Cystoscopy has the highest level of sensitivity and specificity. Cystoscopic findings include small (1-30 mm), solitary, single, soft, pedunculated tumors located in the posterior or lateral walls of the bladder, above the trigone, near the ureteral orifices, or in the urethra, surrounded by hyperemic or normal urothelium that does not penetrate the detrusor. The cystoscopic appearance is identical to that of other low-grade papillary urothelial neoplasms. The exact reason they tend to develop near the ureteral meatuses is unknown; it is thought to be due to local chronic inflammation secondary to recurrent stones, repeated urinary tract infections, and toxins. Surgical treatment of urothelial papillomas, and by extension all small, non-invasive bladder tumors, consists of transurethral resection. It is considered a lesion with a low recurrence rate (7-9%) and an infrequent risk of developing urothelial carcinoma (2-9%)[5]. The median time to progression in reported cases ranges from 84 to 141 months. There are no standardized guidelines on follow-up; however, biannual ultrasound and cystoscopy are useful for detecting residual or recurrent disease. Understanding the biological nature and establishing the correct differential diagnosis are of priority importance for the treatment and prognosis of this rare entity.

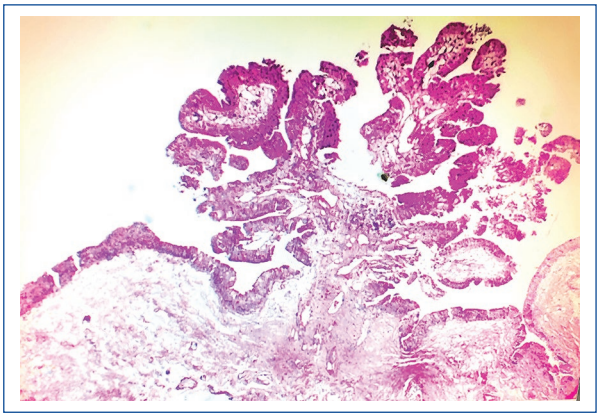

Figure 3. Fibroconnective tissue lined by mature transitional epithelium with a papillary exophytic lesion with simple branches lined by the same type of epithelium.

Conflicts of interest

The authors declare no conflicts of interest.

Funding

None.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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Boletín del Colegio Mexicano de Urología

PERMANYER

CLINICAL CASE

Prostate cancer metastasis to the testis: case report

Metástasis de cáncer de próstata al testículo: reporte de caso

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Abstract

Prostate cancer is one of the leading cancers affecting men worldwide. Only 4% of prostate cancer patients will develop secondary metastases to the testis. The prognosis is poor, and their appearance is often a sign of advanced disease. We present the case of a male patient with metastatic prostate cancer. Testicular metastasis was identified during his oncologic follow-up; the pathology report revealed poorly differentiated adenocarcinoma metastasis. The patient's functional status progressively deteriorated and he died from causes related to his cancer despite multiple lines of treatment. Although there are common sites of recurrence, metastases can occur in uncommon locations, including the testis; any evidence of distant disease should be investigated.

Keywords: *Cancer. Metastasis. Prostate. Testicular tumor.*

Resumen

El cáncer de próstata es uno de los principales tipos de cáncer que afectan a los hombres en todo el mundo. Solo el 4% de los pacientes con cáncer de próstata desarrollarán metástasis secundarias en los testículos. El pronóstico es desfavorable, y su aparición suele ser un signo de enfermedad avanzada. Presentamos el caso de un paciente masculino con cáncer de próstata metastásico. Se identificó una metástasis testicular durante su seguimiento oncológico; el informe de anatomía patológica reveló una metástasis de adenocarcinoma pobremente diferenciado. El estado funcional del paciente se deterioró progresivamente y falleció por causas relacionadas con su cáncer a pesar de haber recibido múltiples líneas de tratamiento. Aunque existen sitios comunes de recurrencia, las metástasis pueden presentarse en localizaciones poco frecuentes, incluidos los testículos; cualquier evidencia de enfermedad a distancia debe ser investigada.

Palabras clave: *Cáncer. Metástasis. Próstata. Tumor testicular.*

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Introduction

Prostate cancer (PCa) is one of the leading cancers affecting men. According to the World Health Organization (WHO), in 2018 there were 1.3 million new cases with 359,000 associated deaths. Secondary tumors to the testis are rare; only 4% of patients with PCa will develop secondary metastases to the testis during their progression.

Possible routes of spread include retrograde venous spread through the spermatic vein, arterial embolism, lymphatic spread through para-aortic lymph nodes, through the vas deferens, transperitoneally through a patent processus vaginalis, and direct invasion.

The time from diagnosis to the appearance of testicular lesions is 2.5 years. Once testicular metastases are diagnosed, the prognosis is poor, and their appearance is usually a sign of advanced disease.

Case report

A 71-year-old hypertensive male was diagnosed with Gleason 7 (3+4) prostate adenocarcinoma by transrectal prostate biopsy and an initial total prostate-specific antigen (PSA) level of 12.1 ng/ml. Classified as having unfavorable intermediate-risk prostate cancer, he underwent a failed radical prostatectomy in a private setting in 2008 for an unknown cause. Only bilateral pelvic lymphadenectomy was performed, with a negative result for adenocarcinoma. He received salvage radiotherapy to the prostate bed and regional nodes. He maintained undetectable PSA levels for 10 years.

During his oncological follow-up, he presented with disease progression with bone metastatic activity identified by bone scintigraphy, for which reason he was referred to our medical center for evaluation and follow-up (2022). Because this patient's treatment was performed at an institution affiliated with ours, the authors declare that they are unaware of other details of his treatment and follow-up. Our institutional approach began in 2022.

At our medical center, we identified a total PSA of 66.54 ng/ml (previous antigen levels are unknown). The institutional PET/PSMA showed tumor activity in the axial and appendicular skeleton (SUVmax 4.47), including the thoracic vertebral bodies, as well as the right iliac bone and both femurs (SUVmax 3.26) (Fig. 1). Based on these findings, the patient was classified as clinical stage IV disease.

In 2022, the patient presented with progressive growth of the right testicle with no other symptoms. Testicular ultrasound revealed a heterogeneous nodular lesion suspicious for malignancy (Fig. 2), with the contralateral testicle within normal range.

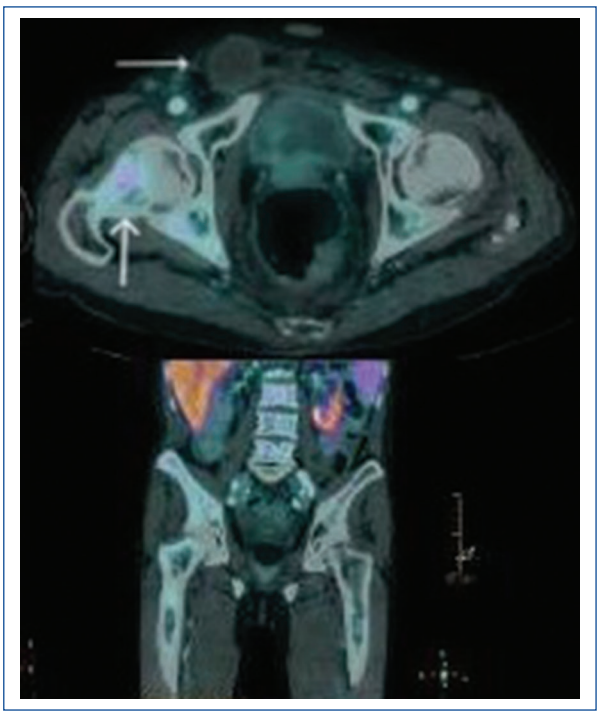

Figure 1. PET/PSMA showing tumor activity in the right femur (thick longitudinal arrow) as well as a right testicular tumor (thin transverse arrow).

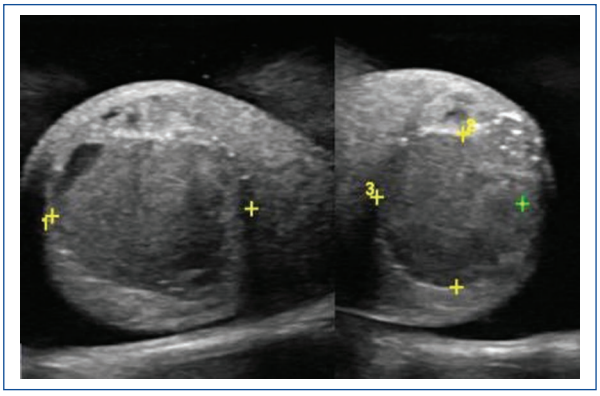

Figure 2. Testicular ultrasound revealing a heterogeneous nodular lesion in the right testicle suspicious for malignancy.

After suspicion of a second primary tumor, a right radical orchiectomy was offered. The pathology report concluded metastasis of poorly differentiated adenocarcinoma (Fig. 3).

He received multiple lines of treatment, including prednisone with abiraterone and docetaxel (2022),

cabazitaxel and enzalutamide (2023), and radium 223 for 6 cycles (2023). He presented with progressive PSA elevation despite multiple options. After radical orchiectomy, there was a slight decrease, however, this was transient (Fig. 4).

Finally, the patient's functional status progressively deteriorated over time and he died at the end of 2023 due to causes related to his oncological disease.

Discussion

Prostate cancer (PCa) is one of the leading cancers affecting men[1]. The development of metastatic disease is one of the main causes of morbidity in PCa[2]. The main sites of metastatic involvement include bones, lymph nodes, lungs, and liver[1].

With the exception of infiltration by leukemia and lymphoma, secondary tumors to the testis are rare[3]. The first documented case of testicular metastasis (TM) was described in 1935[4]. Testicular tumors, based on their origin, can be classified as primary and secondary; primary tumors are more common and tend to occur in younger individuals[1], although testicular non-Hodgkin lymphoma represents the most common primary testicular cancer in men over 60 years of age[5,6].

Metastatic disease to the testes is uncommon due to the blood-testicular barrier and lower scrotal temperature, conditions that may not favor the growth of non-native cells at this site[1]. Only 4% of patients with PCa will develop secondary metastases to the testes during their course[3].

Current literature reports approximately 200 cases of PCa that have developed metastases to the testes. Published case reports suggest that such MTs may present asymptomatic for up to 6 years after PCa diagnosis. The estimated mean time from initial diagnosis to testicular involvement is 4.1 years, with a range from 0 to 15[7].

Routes of spread include venous extension through the spermatic vein, arterial embolism, lymphatic extension via the para-aortic lymph nodes, via the vas deferens, transperitoneally through a patent processus vaginalis, and direct invasion[1]. A possible combination of all the aforementioned routes has been suggested. Bubendorf studied the metastatic route in 1,589 patients diagnosed with PCa at postmortem autopsies, 35% of whom had hematogenous metastases[8].

TMs can be clinically indistinguishable from primary testicular tumors. Radiological diagnosis using scrotal ultrasound is challenging, as the findings mimic primary tumors, particularly mixed germ cell tumors[6,7].

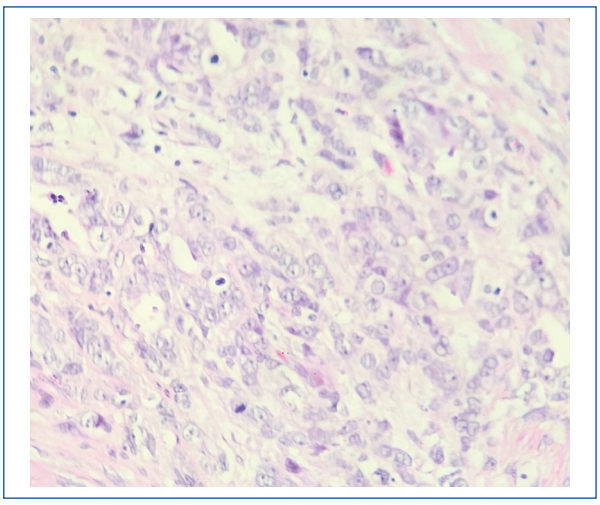

Figure 3. Histological image of the radical orchiectomy showing poorly differentiated acinar adenocarcinoma.

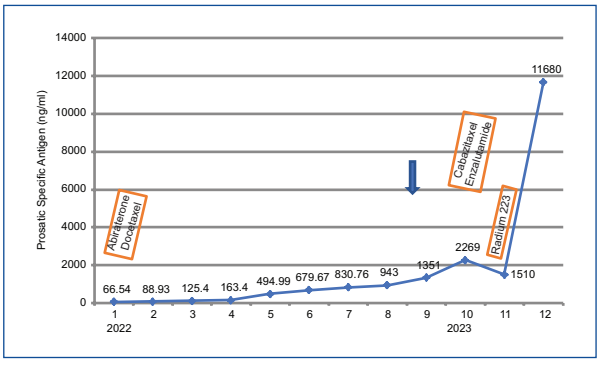

Figure 4. Progressive PSA elevation over time with multiple lines of treatment. The blue arrow represents the time at which testicular metastasis was identified.

Computed tomography combined with positron emission tomography (PET/CT) targeting prostate-specific membrane antigen (PSMA), a transmembrane protein overexpressed in PCa cells, has revolutionized imaging in recent years. This study uses short-lived radionuclides, for example, gallium-68 in the form of [68Ga] Ga-PSMA-11, demonstrating high sensitivity for tumor localization and suspected sites of metastasis after biochemical recurrence[9].

Histologically, TMs are usually similar to the primary prostate tumor, presenting as glandular, cribriform cells without affecting the seminiferous tubules[1]. They can also manifest as a nodular or destructive pattern, affecting and replacing these tubules[8]. Positive immunohistochemical staining for prostate-specific acid phosphatase is often found in these patients, which could help differentiate

metastases from primary cancers[2]. However, with the introduction of luteinizing hormone-regulating hormone (aLHRH) agonists, orchiectomy has been almost completely abandoned, and therefore, detection of this type of disease has become even rarer[10].

Once TM is diagnosed, the prognosis is poor, and its appearance is usually a sign of advanced disease[11]. The average time from diagnosis to the appearance of testicular lesions is 2.5 years. The prognostic implications remain controversial, as fewer than 200 cases have been published in the literature[5]. Due to the rarity of the event, the true long-term impact on overall survival and cancer-specific survival is unknown; The few studies currently available are presented as case reports or small series; therefore, no statistically robust study exists to provide treatment recommendations.

To assist with the decision-making process and patient management, we believe it is important to consider the clinical status, biological characteristics of the tumor, and PSA levels throughout the course of the disease.

Conclusion

MT in PCa is an extremely rare event, and distinguishing it from primary tumors can be difficult. Although there are common sites of metastasis, metastases can occur in uncommon locations. Due to the lack of recommendations in these cases, individualized treatment is required for each patient.

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The authors declare that funding was not received for this study.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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