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EDITORIAL

Ex-voto of Saint Cosmas and Saint Damian: the twin saints and patrons of surgeons

Exvoto de San Cosme y San Damián: los santos cuates, y patrones de los cirujanos

Eduardo A. Hernández-Muñoz[1,2,3], Felipe A. Hernández-López[4], and Erick Sierra-Díaz[5]*

[1]Programa de especialización en Epidemiología, Centro Universitario de Ciencias de la Salud (CUCS), Universidad de Guadalajara, Guadalajara, Jalisco; [2]Servicio de Epidemiología, Unidad de Vigilancia Epidemiológica, Unidad de Medicina Familiar Núm. 53, Instituto Mexicano del Seguro Social, Zapopan, Jalisco; [3]Colegio de Historia y Filosofía de la Medicina del Estado de Guanajuato A.C., León, Guanajuato; [4]Práctica Privada, León, Guanajuato; [5]División de Epidemiología, Unidad Médica de Alta Especialidad, Hospital de Especialidades, Centro Médico Nacional de Occidente, Guadalajara, Jalisco. Mexico

Background

The health-disease process throughout history has had different theoretical models. The conception of religion and magic was widespread in primitive populations, indigenous communities in pre-Columbian times, in the middle ages, and is still present today. This model is based on the existence of spirits or gods and their influence on human affairs. The good ones grant well-being (health, love, and prosperity) and the evil ones punish humanity with natural disasters, diseases, and misfortunes. Magical-religious beliefs in medicine were not exclusive to Central American communities. It was a global phenomenon with cultural variations its representatives were shamans, sorcerers, healers, priests, and spiritualists[1].

The pictorial ex-voto emerged in Italy in the 15th Century and spread throughout Europe arriving in Mexico during the conquest. After the imposition of the Catholic religion, the indigenous cultures abandoned some traditions and beliefs, while others merged with the Spanish. The background of thanking the gods (the latter) remained unchanged; however, the form of doing so underwent a metamorphosis. The votive offerings can be classified by their temporality: a priori (to protect against illness) and a posteriori (in gratitude for healing) in such a way that votive offerings were offered to a saint, virgin, or deity as a coin payment for a favor received[2,3]. During the Spanish-Colonial era (1521-1821), those who made votive offerings were artists with academic training in painting, such as Manuel Arellano, Cristóbal de Villalpando, Tomás Xavier de Peralta, Carlos de Villalpando, and Miguel Cabrera, among others[4]. After independence (1810-1821), votive offerings spread to the middle and lower social classes, when self-taught artists and amateurs began to paint them[5]. About 40 to 70% of the votive themes from the 18th-19th Centuries are relatd to health[2,3].

The "miracle" of Saint Cosmas and Saint Damian

Cosmas and Damian were two brothers (twins) who practiced medicine. It is said that they did not charge for their services. They lived in the port of Aegea, on the bay of Alexandretta in Cilicia (today Çukurova, Turkey). The Roman Emperor Diocletian promoted the worship of the Olympian gods and led the last and one of the bloodiest persecutions against Christians ("The Great Persecution"). Lysias, governor of Cilicia, ordered the imprisonment and torture of Cosmas and Damian who survived the torture and eventually became martyrs

***Correspondence:**
Eduardo A. Hernández-Muñoz
E-mail: eduardoa4m@gmail.com

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Figure 1. Ex-voto to San Cosme and San Damián.

when they were beheaded with their three other brothers (Antony, Leontius, and Euprepius) on September 27, 287 C.E. They were buried in Cyrrhus, Syria. Rumors about the healing power of their relics became popular and Emperor Justinian I (527-565) restored the city and dedicated it to the twin brothers While in Rome, Pope Felix IV (526-530) unified the ancient building of the "Bibliotheca Pacis" to create a Basilica in their honor (Basilica dei Santi Cosma e Damiano). In this library were medical books that were used in a medical school where Galen (129-201 circa c.e.) came to teach[6,7].

In the Golden Legend (*Legenda sanctorum*) by Jacobo de la Vorágine, among the 153 hagiographies, the history of Saint Cosmas and Saint Damian and some of the miracles, they performed are recounted. The two most important are represented in the painting "Miracles of the holy doctors Cosme and Damian" an oil on panel by Fernando del Rincón (1510) located in the Prado Museum in Madrid. The masterpiece shows the miracle of a farmer who while asleep swallowed a snake without realizing it subsequently began to suffer abdominal pain. He went to church and asked the saints about his pain. While praying he fell asleep, and the snake thereafter crawled out. The other and more popular miracle is that of the sacristan of the Basilica dei Santi in Rome who was on the verge of death due to ischemia of a leg, which probably resulted from ergotism, an infection or cancer. In a dream, the saints appeared to him with ointment and surgical instruments to cure him. Before starting, one asked the other: "Where can we get flesh to fill in when we cut away the rotted leg?" The other replied that on the same day, a Moor had been buried in the cemetery. The Saints amputated the leg of the sick man and the corpse and inserted the Moor's leg to the sacristan with ointment. When he awoke, he felt no pain. He lit a candle and saw his leg healed.

He told the story to his relatives and when the miracle was made public, the unbelievers went to the cemetery and opened the Moor's tomb finding the corpse was missing one of his legs, and that next to the rest of his body was the sick leg of the sacristan[8,9]. September 26, (formerly September 27), marks the feast day of St. Cosmas and St. Damian, and as such, they are considered the patron saints of doctors (Fig. 1).

Saint Cosmas and Saint Damian are represented holding boxes with medicine. In the cartouche of the ex-voto, it is stated that Juan Sanchez became ill from a "contagious disease," most likely due to a sexually transmitted infection. However, the votive offerings were public acknowledgments that were hung on the walls of the temples. Therefore, it was best to maintain silence regarding such details.

Funding

None.

Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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EDITORIAL

Exvoto de San Cosme y San Damián: los santos cuates y patrones de los cirujanos

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Eduardo A. Hernández-Muñoz[1,2,3], Felipe A. Hernández-López[4] y Erick Sierra-Díaz[5]*

[1]Programa de especialización en Epidemiología, Centro Universitario de Ciencias de la Salud (CUCS), Universidad de Guadalajara, Guadalajara, Jal.; [2]Servicio de Epidemiología, Unidad de Vigilancia Epidemiológica, Unidad de Medicina Familiar No. 53, Instituto Mexicano del Seguro Social, Zapopan, Jal.; [3]Colegio de Historia y Filosofía de la Medicina del Estado de Guanajuato A.C., León, Gto.; [4]Práctica Privada, León, Gto.; [5]División de Epidemiología, Unidad Médica de Alta Especialidad, Hospital de Especialidades, Centro Médico Nacional de Occidente, Guadalajara, Jal. México

Antecedentes

El proceso de salud-enfermedad a lo largo de la historia ha tenido diversos modelos teóricos. La concepción mágico-religiosa se extendió en las poblaciones primitivas, comunidades indígenas en la época precolombina, en la Edad Media y aún se encuentra presente hasta nuestros días. Este modelo se basa en la existencia de espíritus o dioses y su influencia en el quehacer humano; los buenos conceden bienestar (salud, amor, prosperidad) y los malos castigan a la humanidad con desastres naturales, enfermedades y desgracias. La medicina mágico-religiosa no fue exclusiva de las comunidades centroamericanas, fue un fenómeno global con variaciones culturales y sus representantes fueron chamanes, brujos, curanderos, sacerdotes y espiritistas[1].

El exvoto pictórico surgió en Italia en el siglo XV, se extendió por Europa y llegó a México con la conquista. Posterior a la imposición de la religión católica, las culturas indígenas abandonaron algunas tradiciones y creencias, mientras que otras se fusionaron con las españolas. El fondo de agradecer a los dioses (posteriormente a uno) permaneció inalterado, sin embargo la forma de hacerlo sufrió una metamorfosis. Los exvotos pueden clasificarse por su temporalidad: *a priori* (para protegerse de la enfermedad) y *a posteriori* (en agradecimiento por la curación), de tal forma que los exvotos se ofrecían a un santo, virgen o deidad como una moneda de pago por un favor recibido[2,3]. En el periodo novohispano (1521-1821), quienes realizaban exvotos eran artistas con una formación académica en la pintura como Manuel Arellano, Cristóbal de Villalpando, Tomás Xavier de Peralta, Carlos de Villalpando y Miguel Cabrera, entre otros[4]. Posterior a la independencia (1810-1821), el exvoto se extendió a las clases sociales medias y bajas, cuando autodidactas y aficionados comenzaron a pintarlos[5]. Los temas votivos del siglo XVIII-XIX, en el 40 a 70% se relacionan con la salud[2,3].

El «milagro» de San Cosme y San Damián

Cosme y Damián fueron dos hermanos (gemelos) que ejercieron la medicina, se dice que no cobraban por sus servicios. Habitaron en el puerto de Égea, sobre la bahía de Alejandreta en Cilicia (hoy Çukurova, Turquía). El emperador romano Diocleciano promovía la adoración a los dioses olímpicos y lideró la última y una de las persecuciones más sanguinarias en contra de los cristianos («La Gran Persecución»). Lisias, gobernador de Cilicia, ordenó encarcelar y

***Correspondencia:**
Eduardo A. Hernández-Muñoz
E-mail: eduardoa4m@gmail.com

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Figura 1. Exvoto a San Cosme y San Damián. Óleo sobre lámina de zinc, 36 x 26 cm. Autor desconocido. Colección del autor. A San Cosme y San Damián se les representa sosteniendo unas cajas con medicamento. En la cartela del exvoto se lee que Juan Sánchez enfermó de «enfermedad contagiosa», lo más probable es que se haya debido a una infección de transmisión sexual, sin embargo en los exvotos, al ser agradecimientos públicos, que se colgaban en las paredes de los templos, lo mejor era reservar algunos detalles.

torturar a Cosme y Damián, quienes sobrevivieron a las torturas y finalmente se convirtieron en mártires al morir decapitados con sus otros tres hermanos (Antonio, Leoncio y Euprepio) el 27 de septiembre de 287 e.c. Fueron sepultados en Cirro, Siria. Los rumores sobre el poder de curación de sus reliquias se popularizaron y el Emperador Justiniano I (527-565) restauró la ciudad y la dedicó a los hermanos gemelos, mientras que en Roma el papa Félix IV (526-530) unificó el antiguo edificio de la *Bibliotheca Pacis* para crear una basílica en su honor (*Basilica dei Santi Cosma e Damiano*). En esta biblioteca se encontraban libros de medicina que se utilizaban en una escuela de medicina donde Galeno (129-201 circa e.c.) llegó a impartir clases[6,7].

En la Leyenda áurea (*Legenda sanctorum*) de Jacobo de la Vorágine se relata entre las 153 hagiografías la historia de San Cosme y San Damián y algunos milagros que realizaron. Los dos más importantes se representan en la pintura *Milagros de los santos médicos Cosme y Damián*, un óleo sobre tabla de Fernando del Rincón (1510) ubicada en el Museo del Prado, en Madrid. La obra maestra muestra el milagro de un labrador que estando dormido se tragó una serpiente sin darse cuenta y posteriormente comenzó con dolor abdominal. Fue a la iglesia y pidió a los santos cuates por su dolor y mientras rezaba se quedó dormido y la serpiente salió. El otro milagro, y más popular, es el que aconteció al sacristán de la Basílica de los Santos en Roma, quien se encontraba al borde de la muerte por la isquemia de una pierna, probablemente por ergotismo, una infección o cáncer. En un sueño se le aparecieron los santos con un ungüento e instrumental quirúrgico para curarlo. Antes de iniciar, uno le preguntó al otro: ¿Dónde encontraremos carne sana para colocarla en el lugar que quedará vacío al retirar la enferma? El otro le respondió que ese mismo día habían enterrado a un moro en el cementerio. Los Santos amputaron la pierna al enfermo y al cadáver y unieron la pierna del moro al sacristán con ungüento. Cuando despertó no sintió dolor, prendió una vela y vio su pierna curada. Contó la historia a sus familiares y al hacerse público el milagro, los incrédulos acudieron al cementerio, abrieron la tumba del moro y comprobaron que al cadáver le faltaba una de sus piernas, y que junto al resto de su cuerpo se hallaba la pierna enferma del sacristán[8,9]. En memoria a San Cosme y San Damián se conmemora el día de los cirujanos el 26 de septiembre (antes 27 de septiembre) y se les considera patronos de los cirujanos.

Financiamiento

No hubo financiamiento.

Conflicto de intereses

No existe conflicto de intereses.

Responsabilidades éticas

Protección de personas y animales. Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

Confidencialidad de los datos. Los autores declaran que en este artículo no aparecen datos de pacientes. Además, los autores han reconocido y seguido las recomendaciones según las guías SAGER dependiendo del tipo y naturaleza del estudio.

Derecho a la privacidad y consentimiento informado. Los autores declaran que en este artículo no aparecen datos de pacientes.

Uso de inteligencia artificial para generar textos. Los autores declaran que no han utilizado ningún tipo de inteligencia artificial generativa en la redacción de este manuscrito ni para la creación de figuras, gráficos, tablas o sus correspondientes pies o leyendas.

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ARTÍCULO ORIGINAL

El índice inmunidad-inflamación sistémica preoperatorio como indicador del estadio clínico en el carcinoma de células renales

The preoperative systemic immune-inflammatory index as indicator of clinical stage in renal cell carcinoma

*Abel A. Ricárdez-Espinosa[1], Erick Rojas-Hernández[1], José M. Reyes-Ruiz[2,3], Javier F. Salazar-Angulo[1] y Luis A. Jiménez-López[1,2]**

[1]Departamento de Urología, Unidad Médica de Alta Especialidad, Hospital de Especialidades No. 14, Centro Médico Nacional Adolfo Ruiz Cortines, Instituto Mexicano del Seguro Social (IMSS); [2]Departamento de Educación e Investigación en Salud, Unidad Médica de Alta Especialidad, Hospital de Especialidades No. 14, Centro Médico Nacional Adolfo Ruiz Cortines, IMSS; [3]Facultad de Medicina, Región Veracruz, Universidad Veracruzana. Veracruz, Veracruz, México

Resumen

Objetivo: *Evaluar la utilidad del índice inmunidad-inflamación sistémica (IIS) preoperatorio como predictor en el carcinoma de células renales (CCR) localmente avanzado o metastásico.* **Método:** *Estudio retrospectivo, unicéntrico, observacional y analítico, realizado en un hospital de tercer nivel en Mexico. Se incluyeron pacientes diagnosticados con CCR durante enero de 2021 a julio de 2022 y se estratificaron en CCR localizado (estadio clínico I y II) y CCR localmente avanzado o metastásico (estadio clínico III y IV). Se realizaron análisis de correlación de Spearman, curva ROC (Receiver Operating Characteristic) e índice de Youden.* **Resultados:** *Fueron incluidos 85 pacientes con CCR en estadio clínico I-II (n = 35) y III-IV (n = 50). De ellos, 47 (56%) eran hombres y 38 (44%) mujeres. La mediana de edad de los pacientes en estadio I-II fue de 59.06 (12.433) años y la de los pacientes en estadio III-IV fue de 61.83 (10.001) años (p = 0.416). El IIS se correlacionó con el tamaño del tumor (r = 0.376; p= 0.001) y tuvo un área bajo la curva de 0.77 (intervalo de confianza del 95%: 0.66-0.85; p < 0.0001). El punto de corte óptimo para el IIS fue > 637.2829, con una sensibilidad del 74% y una especificidad del 71.43%.* **Conclusiones:** *Existe correlación entre el IIS y el tamaño del tumor. Por ello, el IIS preoperatorio es un indicador de CCR en estadio clínico III-IV. El IIS es una herramienta clínica efectiva y sencilla en la evaluación preoperatoria de pacientes con diagnóstico de CCR.*

Palabras clave: *Carcinoma de células renales. Índice inmunidad-inflamación sistémica. Valor pronóstico preoperatorio.*

Abstract

Objective: *To evaluate the usefulness of the preoperative systemic immune-inflammatory index (SII) as predictor of locally advanced or metastatic renal cell carcinoma (RCC).* **Method:** *Retrospective, single-center, observational and analytical study performed in a tertiary hospital in Mexico. Patients diagnosed with CRC during January 2021 to July 2022 were included and stratified into localized CRC (clinical stage I and II) and locally advanced or metastatic CRC (clinical stage III and IV). Spearman correlation analysis, receiver operating characteristic (ROC) curve and Youden index were performed.* **Results:** *A total of 85 patients with clinical stage I-II (n = 35) and III-IV (n = 50) CRC were included in the study. Forty-seven patients (56%) were male and thirty-eight (44%) were female. The median age for stage I-II patients was 59.06 (12.433) years and for stage III-IV patients was 61.83 (10.001)*

***Correspondencia:**
Luis A. Jiménez-López
E-mail: luisalfredjimenez@hotmail.com

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years (p = 0.416). IIS correlated with tumor size (r = 0.376; p = 0.001) and had an area under the curve of 0.77 (95% confidence interval: 0.66-0.85; p < 0.0001). The optimal cutoff point for IIS was > 637.2829, with a sensitivity of 74% and a specificity of 71.43%.
Conclusions: *This study demonstrated the correlation between IIS and tumor size. Preoperative IIS could be an indicator of clinical stage III-IV CRC. IIS is an effective and simple clinical tool in the preoperative evaluation of patients diagnosed with CRC.*

Keywords: *Renal cell carcinoma. Systemic immune-inflammatory index. Preoperative prognostic value.*

Introducción

El carcinoma de células renales (CCR) representa aproximadamente el 3% de todos los tumores urológicos, con un estimado de 403,262 nuevos casos y 75,098 defunciones en todo el mundo[1]. La incidencia de CCR ha aumentado anualmente un 3% desde 1970, en relación con el uso sistemático del ultrasonido y la tomografía computarizada durante la evaluación de condiciones abdominales no específicas[2]. En México, de acuerdo con el Global Cancer Obervatory, el CCR se encuentra en el lugar número 11 entre los diferentes tipos de cáncer, con una prevalencia a 5 años de 15,635 casos[3].

La estadificación del CCR es importante para pronosticar las defunciones. En este sentido se emplea el sistema de Fuhrman, pero no es confiable para el subtipo cromófobo y los nuevos subtipos[4]. La Organización Mundial de la Salud (OMS) y la Sociedad Internacional de Patología Urológica han propuesto otros sistemas de estadificación para el CCR[5]. Aun así, son necesarias nuevas herramientas de estadificación con mayores sensibilidad y especificidad que permitan la detección temprana del CCR.

Los linfocitos, los neutrófilos y las plaquetas contribuyen a que las células cancerígenas proliferen e invadan tejidos adyacentes[6]; de esta forma, se asocian con la inflamación y son útiles como predictores del pronóstico de los pacientes[7].

El índice de inmunidad-inflamación sistémica (IIS), un valor obtenido a partir de las cifras de neutrófilos, linfocitos y plaquetas, se asocia con diversos tipos de cáncer, como el cáncer gástrico[8], el carcinoma hepatocelular[9] y el cáncer colorrectal[10]. Un estadio TNM (tumor, nódulos y metástasis) alto y factores histológicos adversos se correlacionan con un pobre pronóstico de sobrevida general[11]. Por lo tanto, el objetivo de este estudio fue evaluar la utilidad del IIS en el pronóstico del CCR.

Método

Diseño del estudio y participantes

Estudio descriptivo, observacional y retrospectivo realizado en pacientes intervenidos con nefrectomía radical, parcial o toma de biopsia en un hospital de tercer nivel (Unidad Médica de Alta Especialidad, Hospital de Especialidades No. 14, Centro Médico Nacional Adolfo Ruiz Cortines), del 1 de enero de 2021 al 31 de julio de 2022. Se excluyeron aquellos pacientes con histología diferente de células claras, enfermedad inflamatoria sistémica, otro tipo de cáncer, enfermedad autoinmunitaria, sida o enfermedad infecciosa. El protocolo del estudio fue aprobado con el número de registro R-2022-3001-121 por el Comité de Ética e Investigación del Hospital, y se realizó siguiendo las consideraciones éticas de la Declaración de Helsinki.

Estadificación de los pacientes

Los tumores se clasificaron según el grado de Fuhrman y la OMS. La evaluación histopatológica se realizó con tinción de hematoxilina y eosina, junto con inmunohistoquímica, necesariamente. El tamaño del tumor se basó en muestras patológicas, como el diámetro mayor en centímetros. Los pacientes fueron clasificados según su estadio clínico en enfermedad localizada (estadios I y II) o localmente avanzada o metastásica (estadios III y IV).

Variables y definiciones

Además de las variables demográficas (sexo, edad y comorbilidad) y de laboratorio (valores de citometría hemática determinados 30 días antes de la intervención quirúrgica) se incluyeron las siguientes variables clínicas: histopatología, grado tumoral, diámetro máximo del tumor, porcentaje de necrosis tumoral, características sarcomatoides e invasión linfovascular.

El IIS se calculó usando la siguiente fórmula: conteo absoluto de neutrófilos × conteo absoluto de linfocitos/conteo absoluto de plaquetas[8].

Análisis estadístico

Las variables cualitativas se expresaron como número y porcentaje, y las variables cuantitativas como media (± desviación estándar) o mediana

Tabla 1. Caracteristicas clínicas de los pacientes con carcinoma de células renales estratificados según su estadio clínico

Variable	Estádio clínico I y II (n = 35)	Estádio clínico III y IV (n = 50)	Valor de p
Edad, años	59.06 (12.433)	61.83 (10.001)	0.416
Sexo, femenino	15 (17.6%)	23 (27.1%)	0.774
IMC	28.30 (5.41)	27.78 (4.95)	0.440
Diabetes	7 (8.2%)	17 (20%)	0.158
HAS	19 (22.4%)	31 (36.5%)	0.447
Tabaquismo	18 (21.4%)	23 (27.4%)	0.685
Necrosis tumoral	18 (22%)	34 (41%)	0.052
Características sarcomatoides	1 (1.2%)	11 (13.4%)	0.009*
Invasión linfovascular	0 (0%)	20 (24%)	< 0.001*
Neutrófilos ($x10^3/\mu L$)	4.44 (1.51)	5.22 (1.96)	0.021*
Linfocitos ($x10^3/\mu L$)	2.25 (0.788)	1.82 (0.769)	0.001*
Plaquetas ($x10^3/\mu L$)	251 (72.945)	327 (133.113)	0.010*
Monocitos ($x10^3/\mu L$)	0.59 (0.227)	0.69 (0.248)	0.103
Tamaño del tumor, cm	5.5 (3)	9.5 (3)	< 0.0001*
IIS	547.14 (286.4)	1083.91 (725.7)	< 0.001*

(rango intercuartil). La asociación entre las variables cualitativas se determinó mediante la prueba de χ^2 o la prueba exacta de Fisher. Las variables cuantitativas se compararon entre los grupos usando la prueba t de Student cuando tuvieron una distribución normal o paramétrica, y la prueba U de Mann-Whitney cuando la distribución de los datos fue no normal o no paramétrica. Se realizó una curva ROC *(Receiver Operating Characteristic)* para determinar la precisión del IIS en la predicción del CCR en estadio localmente avanzado o metastásico. El índice de Youden se utilizó para determinar el punto de corte óptimo del IIS. Se consideró un valor de $p < 0.005$ como diferencia estadísticamente significativa. Los datos se analizaron con los programas estadísticos SPSS v25 y MedCalc 18.11.

Resultados

Se incluyeron 85 pacientes con CCR que fueron estratificados por su estadio clínico: 35 en estadio I-II y 50 en estadio III-IV. Sus características demográficas, clínicas y de laboratorio se muestran en la tabla 1. Del total de los pacientes, 47 (56%) eran hombres y 38 (44%) eran mujeres. La mediana de edad de los pacientes con estadio I-II fue de 59.06 (12.433) años y la de los pacientes es estadio III-IV fue de 61.83 (10.001) años ($p = 0.416$). El índice de masa corporal, la diabetes *mellitus,* la hipertensión arterial y el tabaquismo no tuvieron diferencias estadísticamente significativas ($p > 0.05$) cuando se comparados entre los grupos de estudio. Los pacientes en estadio III-IV tuvieron necrosis tumoral, características sarcomatoides e invasión linfovascular en un 41% (n = 34), un 13.4% (n = 11) y un 24% (n = 20), respectivamente. Los niveles de neutrófilos y de plaquetas, y el IIS, estuvieron elevados significativamente ($p < 0.001$) en el grupo de pacientes en estadio III-IV en comparación con aquellos en estadio I-II (Tabla 1).

Los valores del IIS se correlacionaron con el tamaño del tumor ($r = 0.376$; intervalo de confianza del 95% [IC95%]: 0.161-0.556; $p = 0.001$) (Fig. 1). Para determinar el valor predictivo del IIS en la detección de CCR localmente avanzado o metastásico (estadio clínico III-IV) se realizó una curva ROC y el AUC fue de 0.77 (IC95%: 0.66-0.85; $p < 0.0001$) (Fig. 2). El índice de Youden ($J = 0.45$) reveló que el punto de corte óptimo para el IIS fue > 637.2829, con una sensibilidad del 74% y una especificidad del 71.43% (Tabla 2).

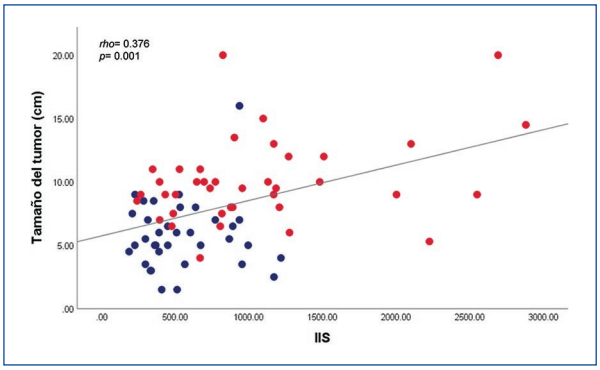

Figura 1. Análisis de correlación entre el IIS y el tamaño del tumor. Los puntos de color azul indican los pacientes en estadio clínico I-II y los de color rojo los pacientes en estadio clínico III-IV.

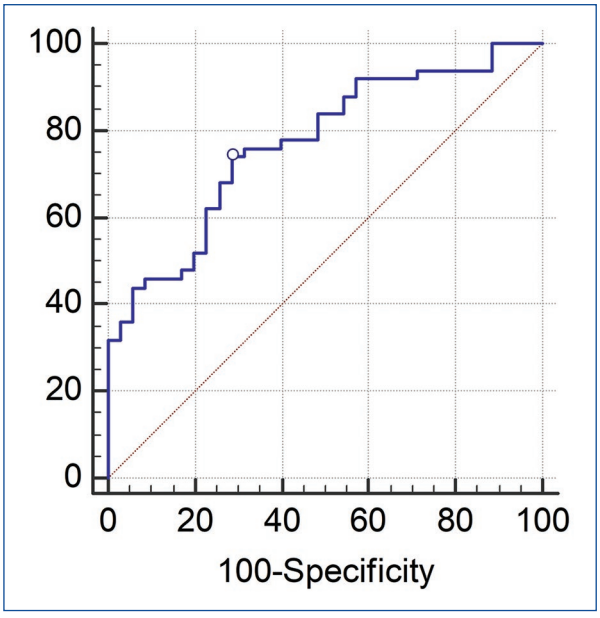

Figura 2. Curva ROC para la determinación de la precisión del IIS en la predicción del CCR en estadio clínico III-IV.

Discusión

En este estudio evaluamos el uso del IIS como predictor del subtipo histológico de acuerdo con la World Health Organization Heidelberg (WHOH), el estadio clínico avanzado definido por el American Joint Committee on Cancer (AJCC) y el grado tumoral de acuerdo con el sistema de estadificación de Fuhrman. Hasta este momento no está descrito el mecanismo por el cual el IIS afecta el pronóstico del cáncer, pero se conocen los tres biomarcadores inflamatorios

Tabla 2. Valor del índice inmunidad-inflamación sistémica como predictor de factores histopatológicos de mal pronóstico

Variable	AUC	IC	Valor de p
Necrosis tumoral	0.669	0.550 a 0.774	0.052
Patrón sarcomatoide	0.778	0.667 a 0.867	0.001
Grado tumoral de la OMS	0.721	0.605 a 0.819	0.0010

involucrados. Los neutrófilos secretan factores inflamatorios, como interleucinas 6 y 10, prostaglandinas y factores de crecimiento endotelial vascular, que cumplen la función de acelerar la formación del microambiente tumoral que dará lugar a la angiogénesis, precipitando así la adhesión de células tumorales y metástasis a distancia. Por otra parte, las plaquetas realizan la función de protección de células tumorales adyacentes, evitando ataques inmunitarios exógenos y endógenos, lo que lleva a la multiplicación e invasión de estas[12]. Además, también se liberan citocinas que actúan de manera similar a los neutrófilos. Por último, los linfocitos infiltrados en el tumor conducen a la apoptosis de células tumorales, las cuales se eliminan a través del sistema de inmunidad celular y humoral.

Por ello, un IIS alto está indirectamente vinculado con una función inmunitaria deficiente y un aumento de la capacidad de invasión tumoral, resultando un útil predictor de características histopatológicas de mal pronóstico y estadio clínico.

Un metaanálisis conducido por Li et al.[13] incluyó 13 escritos con 3974 pacientes, desde 2016 hasta 2020, y evidenció la asociación del IIS preoperatorio y variables como sobrevida y supervivencia. Se demostró que un IIS preoperatorio alto indicaba peor sobrevida general ($p = 0.001$), supervivencia libre de progresión ($p = 0.002$) y supervivencia especifica ($p < 0.001$), destacando que el punto de corte fue distinto en cada estudio. Adicionalmente, estos pacientes con un IIS elevado mostraban factores histopatológicos de alto riesgo de metástasis ($p < 0.001$), tamaño tumoral mayor ($p < 0.001$), grado tumoral pobremente diferenciado ($p < 0.001$) y etapa clínica avanzada ($p < 0.001$). En nuestro estudio, las características histopatológicas de mal pronóstico en ambas poblaciones fueron la presencia de diferenciación sarcomatoide ($p < 0.001$), necrosis tumoral ($p = 0.052$), invasión linfovascular ($p < 0.001$) y grado tumoral alto, así como gran tamaño tumoral.

Chang et al.[14] realizaron un estudio retrospectivo en el que incluyeron 441 pacientes. Definieron un IIS con

decremento de la albumina < 40 g e índice linfocitos-monocitos < 0.44, y observaron una asociación con un tamaño tumoral > 5 cm (p = 0.017 y p = 0.02, respectivamente), presencia de necrosis tumoral (p < 0.001 y p = 0.001) y presencia de invasión linfovascular (p = 0.034 y p = 0.025). En este estudio, el IIS > 637.282 tuvo relación con factores de mal pronóstico histopatológicos, como el diámetro (p = 0.0010), el grado tumoral según la OMS (p = 0.0010) y el estadio clínico (p = 0.0012), demostrando relación con otros índices.

Ozbek et al.[15] realizaron un estudio retrospectivo utilizando el IIS en 176 pacientes con diagnóstico de CCR sometidos a nefrectomía radical. Hallaron una correlación positiva entre el tamaño tumoral y el IIS (p = 0.03), así como una relación inversamente proporcional entre la supervivencia en meses y un IIS elevado (p = 0.006). Además, los tumores de alto grado (G3 y G4) según la estadificación de Fuhrman tuvieron relación con un IIS mayor (997.57 ± 720.10), comparados con los tumores de bajo grado (687.43 ± 515.96). Los resultados obtenidos en este estudio correlacionaron la enfermedad localizada (G1 y G2) y la enfermedad avanzada (G3 y G4), obteniendo valores de corte > 637 con una sensibilidad del 74.00% y una especificidad de 71.43%.

El IIS resulta factible de utilizar y económico, por lo que ha sido propuesto destacando su uso práctico con el conteo de neutrófilos, plaquetas y linfocitos. Cabe señalar que no existe un valor estándar para un punto de corte del IIS, el cual varía en los diferentes estudios, y por lo tanto es necesario realizar estudios prospectivos y multicéntricos para identificar un valor de punto de corte estándar.

Conclusiones

En conjunto, nuestros hallazgos sugieren que el IIS se correlaciona con el tamaño del tumor y además podría ser un predictor de CCR localmente avanzado (estadios clínicos III-IV). Se necesitan más estudios en población mexicana para poder establecer un punto de corte en nuestra población.

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Los autores declaran no tener conflicto de intereses.

Responsabilidades éticas

Protección de personas y animales. Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

Confidencialidad de los datos. Los autores declaran que en este artículo no aparecen datos de pacientes. Además, los autores han reconocido y seguido las recomendaciones según las guías SAGER dependiendo del tipo y naturaleza del estudio.

Derecho a la privacidad y consentimiento informado. Los autores declaran que en este artículo no aparecen datos de pacientes.

Uso de inteligencia artificial para generar textos. Los autores declaran que no han utilizado ningún tipo de inteligencia artificial generativa en la redacción de este manuscrito ni para la creación de figuras, gráficos, tablas o sus correspondientes pies o leyendas.

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REVIEW ARTICLE

Understanding prostate cancer stem cells: implications for therapy and treatment resistance

Comprensión de las células madre del cáncer de próstata: implicaciones para la terapia y la resistencia al tratamiento

*Ana K. Flores-Islas[1], Cecilia Rico-Fuentes[2], Said Castro-Zazueta[3], Erick Sierra-Diaz[4,5], Ana L. Pereira-Suárez[6,7], Mariel García-Chagollán[7], and Jorge A. Ramírez-de-Arellano[7]**

[1]Faculty of Biomedical Sciences, Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara, Guadalajara; [2]Biosciences Faculty, Centro Universitario de los Altos, Universidad de Guadalajara, Tepatitlán de Morelos; [3]Department or Service, Hospital Ángeles del Carmen, Guadalajara; [4]Department of Urology, Hospital de Especialidades Centro Médico Nacional de Occidente, Guadalajara; [5]Department of Surgical Clinics and Public Health, Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara, Guadalajara; [6]Department of Microbiology and Pathology, Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara, Guadalajara; [7]Department of Molecular and Genomics, Instituto de Investigación en Ciencias Biomédicas, Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara; Jalisco, Mexico

Abstract

Prostate cancer (PCa) is a highly heterogeneous and rapidly progressing malignancy with a complex etiology. The presence of cancer stem cells (CSCs) within prostate tumors contributes to treatment resistance, relapses, and metastasis. Understanding the molecular mechanisms and signaling pathways involved in CSC regulation is crucial for developing effective therapies. This article highlights the role of CSCs, particularly PCa stem cells (PCSCs), in PCa initiation and progression. It discusses the cellular heterogeneity of prostate tumors, the theories of clonal evolution and CSCs, and the resistance mechanisms exhibited by CSCs. In addition, the involvement of signaling pathways such as Hedgehog, PI3K/AKT, and mitogen-activated protein kinase/extracellular regulated kinases in PCSC regulation is explored. The need for new therapies targeting CSCs is emphasized, and potential treatment approaches, including immunotherapy and genetic engineering, are discussed. Despite the challenges posed by advanced therapies, targeting PCSCs holds promise for improving patient outcomes in advanced PCa. Further research on PCSC biology is warranted to advance our understanding and develop more effective therapeutic strategies.

Keywords: *Prostate cancer. Prostate cancer stem cells. Hedgehog. PI3K. Mitogen-activated protein kinase.*

Resumen

El cáncer de próstata (CaP) es una neoplasia maligna altamente heterogénea y de rápido progreso con una etiología compleja. La presencia de células madre cancerosas (CSC) dentro de los tumores de próstata contribuye a la resistencia al tratamiento, las recaídas y la metástasis. Comprender los mecanismos moleculares y las vías de señalización involucradas en la regulación de CSC es crucial para desarrollar terapias efectivas. Este artículo destaca el papel de las CSC, en particular las CSC de próstata (PCSC), en el inicio y la progresión del CaP. Discute la heterogeneidad celular de los tumores de próstata, las teorías de la evolución clonal y las CSC, y los mecanismos de resistencia exhibidos por las CSC. Además, se explora la participación de vías de señalización como Hedgehog, PI3K/AKT y MAPK/ERK en la regulación de PCSC.

***Correspondence:**
Jorge A. Ramírez de Arellano-Sánchez
E-mail: adrian.ramirez@academicos.udg.mx

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Se enfatiza la necesidad de nuevas terapias dirigidas a las CSC y se analizan posibles enfoques de tratamiento, como inmunoterapia e ingeniería genética. A pesar de los desafíos que plantean las terapias avanzadas, apuntar a las PCSC promete mejorar los resultados de pacientes con CaP avanzado. Se justifica una mayor investigación sobre la biología de PCSC para avanzar en nuestra comprensión y desarrollar estrategias terapéuticas más efectivas.

Palabras clave: *Cáncer de próstata. Células troncales de cáncer de próstata. Hedgehog. PI3K. Mitogen-activated protein kinase.*

Introduction

Prostate cancer (PCa) is a highly heterogeneous and rapidly progressing malignancy with an unknown etiology. However, it is believed that several triggers and risk factors may exist, with advanced age being the most significant one[1,2]. Globally and nationally, PCa has the highest incidence among men over 60 years old[3]. The majority of PCa cases are detected in early stages, and with the availability of increasingly effective therapies, survival rates have improved in recent years. However, there is also a tendency for rapid progression, leading to treatment-resistant cancer, relapses, and a high metastatic potential. This indicates that there is still much to understand about the initiation and progression of PCa[4].

The high cellular heterogeneity of prostate tumors is thought to contribute to the eventual treatment failures, as therapies are not targeted toward all cellular entities. Different cell types respond differently to treatments due to varying degrees of sensitivity[5]. Over the years, models have been developed to explain the diversity of cells observed in malignant tumors, with clonal evolution and cancer stem cells (CSCs) being the most commonly employed models. The clonal evolution theory, also known as the mutation hypothesis, suggests that a single cell accumulates a series of mutations over time, acquiring malignant properties and forming tumors. However, this theory seems inaccurate as mutations are not always the main causal event in the occurrence and development of cancer[6]. On the other hand, the cancer stem cell theory is one of the most accepted hypotheses to explain relapses due to the residual presence of a population of cells called CSCs. These cells share characteristics with stem cells, which are associated with a more aggressive phenotype and metastatic potential[7]. This theory suggests that tumor initiation and progression result from the conversion of normal cells into CSCs, with only this subpopulation having the capacity to develop carcinogenic processes[6].

Clinical evidence suggests that resistance and relapses may not be solely due to the phenotypic alterations inherent to cancer, but rather to the presence of CSCs. Therefore, targeting therapies toward CSCs could represent a promising therapeutic approach.

Discussion

Prostate cancer (PCa) stem cells: what are they?

Stem cells possess the ability to self-renew, migrate, and differentiate into any type of mature cell[8]. It is believed that when stem cells acquire a malignant phenotype, they become CSCs, which may be responsible for treatment resistance, relapses, and metastasis due to their shared characteristics with stem cells. CSCs can generate malignant neoplasms by self-renewing and differentiating into various cellular subtypes[8-10]. Several events have been proposed to induce the transformation of stem cells into CSCs, including the accumulation of chromosomal abnormalities, amplified expression of c-Myc, elevated telomerase activity, and p53 mutations[8,11,12].

CSCs were first observed in 1937 by Furth and Kahn, who determined the number of cells necessary to transmit malignant leukemia tumors in mice[13]. It is believed that CSC populations are present in all cancers but in very low proportions[8,14]. In PCa, PCa stem cells (PCSCs) represent approximately 0.1% of the tumor cell population[15]. Although a minority, this cell subset possesses characteristics that allow it to survive conventional therapies and generate new tumors through its ability to self-renew and differentiate into various cell types[9]. PCSCs exhibit drug resistance due to the expression of ATP-dependent membrane transporter proteins, which are known to be resistant to a wide range of drugs[9,16]. Some studies indicate resistance to chemotherapy drugs due to aldehyde dehydrogenase (ALDH), a marker present in many CSCs, eliminating the radicals produced by oxidative stress generated by these treatments. ALDH also eliminates the free radicals produced by radiotherapy, resulting in resistance to these therapeutic options[17,18]. Furthermore, PCSCs have the ability to repair DNA damage caused by chemotherapy and radiotherapy, thereby protecting cancer

cells from apoptosis[19]. At least five mechanisms have been observed through which CSCs exhibit resistance to chemotherapy: maintaining an inactive proliferative state by exiting the cell cycle, activating drug efflux mechanisms, overexpressing DNA repair mechanisms, overexpressing anti-apoptotic genes, and releasing cytokines that make other cells in their tumor microenvironment resistant to therapy[14].

Due to the high incidence and mortality of PCa in the male population and the growing body of evidence supporting the role of PCSCs in the initiation and progression of PCa due to their adaptable characteristics within the tumor microenvironment and resistance to current treatments, directing attention to understanding the molecular biology of this cell subset is promising for the search and development of more effective therapies.

In addition, several signaling pathways are responsible for regulating self-renewal and differentiation of stem cells. Failures in these pathways can promote their conversion to CSCs, leading to tumorigenesis[9]. PCSCs are capable of activating survival signaling pathways and repressing apoptosis pathways, making them highly adaptable to their microenvironment[10].

Hedgehog: the Hedgehog signaling pathway is a highly conserved and regulated pathway that plays a critical role in cell proliferation, cell-cell interaction, and embryonic development[20-22]. This pathway is involved in all aspects of cancer development, including the development of CSCs[20,23]. Several studies have linked the Hedgehog pathway to PCa and PCSCs. For example, a study by Chang et al. demonstrated that aberrant activation of the pathway promoted the transformation from stem cells to PCSCs[24]. Another study by Zhou et al. in 2023 provided evidence of the significant role of the Hh pathway in PCa evolution and the origin and development of PCSCs, showing active Hh ligand in p63+ cells, which is related to PCSCs due to their phenotype[10].

PI3K: The PI3K/Akt/mTOR pathway is involved in cell differentiation, cell growth, cell cycle progression, endocytosis, motility, apoptosis, intermediate metabolism, and angiogenesis[25]. Evidence suggests that its overactivation facilitates tumor formation, disease progression, and therapeutic resistance in PCa[26]. The results obtained by Chang et al. support the relationship between PI3K/AKT and PCSCs, as the PCSC stemness phenotype is regulated by this pathway[27].

Mitogen-activated protein kinase (MAPK): MAPK pathway is involved in cell growth, differentiation, proliferation, and cell death[28]. It is one of the most studied pathways in cancer due to its significant involvement in mitogenic signaling[29-31]. An analysis of differentially expressed genes in cellular subpopulations of castration-resistant PCa (CRPC) using the Kyoto Encyclopedia of Genes and Genomes pathway analysis by Zhou et al.[10] revealed that MAPK pathway activation could potentially regulate the generation of PCSCs.

Since CSCs are regulated by multiple signaling pathways and transcription factors, studying their dysregulation, effects, and implications represents a promising therapeutic target[9].

The need for new therapies

Since their identification in 1994, CSCs have been considered a promising target for the development of more effective therapies[9]. The high cellular heterogeneity present in prostate tumors causes each subpopulation to respond differently to treatments, including PCSCs. Despite representing <1% of the tumor cell population, the remaining cells that were not eliminated by conventional therapies due to their resistance proliferate and form new tumors, leading to relapses. Current treatments generally have initial success in early-stage disease, with nearly 100% 5-year survival rates for localized PCa. However, the disease can progress to CRPC after 2-3 years of androgen deprivation therapy (ADT), and when it becomes metastatic, the 5-year survival rate decreases to around 30%[10].

Treatment selection depends on parameters such as age, risk group, clinical stage, and androgen response status of tumors[28]. Treatment options include active surveillance without treatment for low-risk PCa, solitary or combined ADT, chemotherapy, bone-targeted therapy, and radiation therapy for advanced stages. Additional forms of treatment such as abiraterone and enzalutamide are recommended when PCa or CRPC does not respond to traditional hormonal therapy[5]. Radio-ligand therapy for metastatic CRPC combined with the standard regimen has recently been approved in the United States[4,32]. Targeting PCSCs is a promising strategy for the treatment of advanced, systemic, and irreversible PCa. Therefore, in addition to these options, therapies focused on PCSCs are currently being explored, including immunotherapy, miRNA use, nanotechnology, CRISPR/Cas9, and photothermal ablation therapy[33].

Immunotherapy could have better tolerability compared to chemotherapy or hormonal therapy since it utilizes the patient's immune system to fight cancer cells[34]. Immunotherapies include the use of antibodies,

immune cells, vaccines, and chimeric antigen receptor T-cell (CAR-T) therapies[33]. Vaccination with prostate stem cell antigen, which is overexpressed in metastatic tissues, has shown promising results in inducing protective immune responses mediated by CD4+ and CD8+ T cells in advanced PCa[35]. Sipuleucel-T, a dendritic cell-based vaccine, was approved in 2010 for use in the treatment of metastatic CRPC. It demonstrated a relative reduction in the risk of death of 22% compared to the placebo group[34,36,37]. Another vaccine, PSA-TRICOM (Prostvac®), did not show effects on overall survival or patients alive without events in metastatic CRPC when used as monotherapy in Phase III clinical trials. However, it is being explored in combination with docetaxel and enzalutamide[34,38]. CAR-T cell therapy is also being studied as a potential treatment for advanced PCa and is currently in Phase I clinical trials[34]. This therapy can be designed according to specific antigens by introducing genetic engineering into the patient's T cells through *in vitro* transduction[35].

However, there are several challenges with advanced and emerging therapies, including their high costs. For example, CAR-T cell therapy, which has been approved by the FDA for blood cancers, can exceed $450,000[39].

Conclusion

Given the above, PCSCs represent a studied target with broad therapeutic potential in PCa, particularly for patients with aggressive PCa. Therapies specifically targeting this cell subset could prevent a decline in patients' quality of life, treatment resistance, comorbidities, relapses, or reduced life expectancy. Therefore, further in-depth study of PCSC biology is warranted.

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Conflicts of interest

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

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appears in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appears in this article.

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REVIEW ARTICLE

Key role of myeloid-derived suppressor cells in cancer: perspectives and therapeutic opportunities in prostate cancer

Rol clave en células supresoras de origen mieloide en cáncer: perspectivas y oportunidades terapéuticas en cáncer de próstata

Pedro Martínez-Reyes[1], Erick Sierra-Díaz[2,3], Alejandro Bravo-Cuellar[4], Jose L. Sandoval-Tamayo[3], Guillermo Sánchez-Villaseñor[3], and Pablo C. Ortiz-Lazareno[4]*

[1]Department of Physiology, Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara; [2]Epidemiology Division, Unidad Médica de Alta Especialidad, Hospital de Especialidades, Centro Médico Nacional de Occidente; [3]Immunology Division, Centro de Investigación Biomédica de Occidente; [4]Department of Urology, Unidad Médica de Alta Especialida, Hospital de Especialidades, Centro Médico Nacional de Occidente. Guadalajara, Jalisco, Mexico

Abstract

Prostate cancer is one of the most common solid tumor bases, according to data from the World Health Organization. Over the past few years, its incidence and prevalence rates have increased significantly and have become a public health concern. Mortality and financial issues are worrisome since health systems around the world consider prostate cancer a major problem in future. Based on this health threat, interest has arisen on several research fronts to get more knowledge about the therapeutic options in fields such as endocrine pathways, molecular biology, and immunology. The present work aims to report on some perspectives for prostate cancer treatment based on the role of myeloid-derived suppressor cells and its primary importance, due to the central position, it plays in the tumor microenvironment.

Keywords: *Prostate cancer. Myeloid-derived suppressor cells. Management. Tumor microenvironment.*

Resumen

El cáncer de próstata es una de las bases tumorales sólidas más comunes, según datos de la Organización Mundial de la Salud. En los últimos años, sus tasas de incidencia y prevalencia han aumentado significativamente y se han convertido en un problema de salud pública. La mortalidad y las cuestiones financieras son preocupantes, ya que los sistemas de salud de todo el mundo consideran que el cáncer de próstata será un problema importante en el futuro. A partir de esta amenaza para la salud, ha surgido interés en varios frentes de investigación para obtener más conocimiento sobre las opciones terapéuticas en campos como las vías endocrinas, la biología molecular y la inmunología. El presente trabajo tiene como objetivo informar sobre algunas perspectivas para el tratamiento del cáncer de próstata basadas en el papel de las células supresoras derivadas de mieloides y su importancia primordial, debido a la posición central que desempeñan en el microambiente tumoral.

Palabras clave: *Cáncer de próstata. Células supresoras de origen mieloide. Terapéutica. Microambiente tumoral.*

Correspondence:
Erick Sierra-Diaz
E-mail: erksland@hotmail.com

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Introduction

Prostate cancer is defined as the uncontrolled proliferation of epithelial cells (secretory columnar cells, basal cells, and rare neuroendocrine cells) of the prostate gland[1]. It is the malignant neoplasm with the highest incidence and mortality in Mexican adult males[2]. In most cases, this cancer originates in the columnar cells of the prostate epithelium. A family history of prostate cancer, being of African descent, and of advanced age, have all been identified as risk factors[1]. Another factor that influences the development of prostate cancer and other types of cancer is alterations in the processes of immunosurveillance and immunoediting, because of the interaction between immune cells and tumor cells[3]. The cells involved in the immunoediting process are cytotoxic T lymphocytes (CTLs), helper T lymphocytes, regulatory T lymphocytes, neutrophils, dendritic cells, NK cells, macrophages, and myeloid-derived suppressor cells (MDSC), among others[3,4].

Immunoediting theory

In 1970, Frank Macfarlane Burnet proposed that immunosurveillance is a mechanism by which potentially dangerous mutant cells are eliminated or inactivated and that this process is immunological in nature[5]. Subsequently, Robert D. Schreiber and his co-workers wondered why immunocompetent individuals develop cancer even when the immunosurveillance process is present[6]. This questioning led to the inference that the immunosurveillance process was inefficient or incomplete. Because of this, researchers proposed the model or theory of immunoediting, which is described as a much more complex process than immunosurveillance, and that the immune system exerts a cancer-destroying effect, but also exerts a cancer-promoting effect that favors cancer cell survival[6].

The immunoediting process is divided into three phases: elimination, equilibrium, and escape. Elimination is the phase in which immunosurveillance is involved[3,4,6]. The concept of immunosurveillance refers to the process in which immune cells, particularly CTLs and NK cells, constitutively monitor tissue cells to identify alterations that indicate damage or infection, and if they encounter an abnormality, they exert their cytotoxic function to eliminate the threat[6].

Immunosurveillance has beneficial and detrimental consequences. The destruction of cancer cells that express immunogenic antigens culminates in the survival of those cells are poorly immunogenic antigens, so that the immune system does not recognize them. The immediate consequence is that some tumor cells are eliminated, but others continue to live and proliferate[3,6,7].

The second phase is the equilibrium phase. Once the immune system has exerted selective pressure on the tumor cells, a state of equilibrium is reached in which the cancer cells are dormant and the immune system suppresses their proliferation[3,6,7].

In the escape phase, the “edited” tumor cells, with low immunogenicity, begin to proliferate progressively, since the immune cells do not have the capacity to identify and destroy them[3,6,7].

The tumor microenvironment

Multiple cell types constitute the tumor microenvironment, such as cancer cells themselves, stromal cells, endothelial cells, and immune system cells. Each cell type interacts in some way in the microenvironment[8]. Solid tumors, such as prostate cancer, can be simply classified into two types: immunologically cold and immunologically hot[9].

The immunologically cold tumor is one that has little T-lymphocyte infiltration and little inflammation caused by T-lymphocytes. The warm tumor is the opposite, with abundant infiltration of activated T-lymphocytes and inflammation[9].

Prostate cancer is characterized by a low CD8+ T-lymphocyte infiltration and low tumor mutational burden and is therefore considered a cold solid tumor[8]. Cold tumors tend to respond poorly to immunotherapy. This is due in part to low T-lymphocyte infiltration in the tumor microenvironment[10].

It has been identified that the T cell effector function is diminished or inhibited in the tumor microenvironment. This inhibition is the result of the effect of cells with immunosuppressive properties such as cancer-associated macrophages, regulatory T cells, and MDSCs[11].

Soluble factors that regulate and also form part of the tumor microenvironment include cytokines, chemokines, and metabolites such as amino acids, ATP, and adenosine. These soluble factors act in an autocrine, paracrine, or endocrine manner[11].

MDSCs play a key role in the tumor microenvironment. These cells interact directly (cell-cell contact) and indirectly (secretion of soluble factors and metabolite depletion) with cancer cells and cells of the immune system[12,13]. MDSC-mediated immunosuppression occurs at multiple levels of immune system function,

including inhibition of T lymphocytes through metabolite depletion[14], induction of proliferation, and differentiation (expansion) of regulatory T cells[15], which inherently suppress the antitumor immune response. MDSCs also interfere with T-cell activation and proliferation with increased levels of TGF-β, IL-10, and decreased IFN-γ. These findings reflect a T cells humoral immune response in an immunosuppresive environment[16].

Myeloid-derived suppressor cells

MDSC are myeloid cells that have not completed the maturation process, and consequently, they trigger multiple immunoregulatory effects[17]. In physiological conditions, myeloid suppressor cells regulate the immune response to avoid excessive tissue damage. In pathological conditions such as cancer, the functions of these cells tend to enhance the evasion of immune destruction[17].

Hematopoietic stem cells (HSC) give rise to all hematopoietic cells, including MDSC, the process by which these cells are generated, and it is known as emergency myelopoiesis, which represents a rapid and altered myelopoiesis in response to a noxious stimulus[17]. In this process, the phenotype of the suppressor cells of myeloid origin is intermediate between the phenotype of HSCs and that of monocytes or granulocytes. For emergency myelopoiesis to occur, an inducer is required, such as tissue damage or infection. The purpose of the physiological response mechanism is to neutralize the threat that is present in the host through the production of myeloid cells[17,18].

Chronic inflammation that occurs in pathological conditions such as cancer, chronic infections, and autoimmune diseases constitutes a persistent inducer of emergency myelopoiesis[18]. Persistent inflammation prevents immature myeloid cells (IMCs) from acquiring their final monocyte or granulocyte phenotype, resulting in the generation of suppressor cells of myeloid origin[17,18].

Three subtypes or lines of suppressor cells of myeloid origin (MDSC) have been identified. Those with a phenotype similar to polymorphonuclear cells or granulocytes (PMN-MDSC) are identified as CD33+, CD11b+, HLA-DR-, Lin- (CD3-, CD19-, CD20-, CD56-), CD15+, CD14-. Monocyte-like phenotypes (M-MDSC) are identified as CD33+, CD11b+, HLA-DR-, Lin- (CD3-, CD19-, CD20-, CD56-), CD15-, CD14+. Finally, the e-MDSC (early-MDSC) are considered as early or immature MDSC and are identified as the two which were previously mentioned, with the difference being double negative, that is, CD14- and CD15-[19,20].

Immunosuppressive mechanisms of MDSCS

Contact inhibition

MDSCs have been shown to express multiple immune checkpoints such as PD-L1, CD155, VISTA, Galectin-9, and FasL. The interaction of these molecules with their cognate ligand-receptor on the surface of the T cell induces their anergy or apoptosis[18].

MDSCs also express CTLA-4[18] blockade with ipilimumab. This molecule has been shown to reduce PMN-MDSC levels in the peripheral blood of patients with metastatic melanoma and reduce the production of arginase-1 synthesized by these cells[21].

Surface-based galectin-9 interacts with TIM-3 on human T cells. This interaction produces the expansion of MDSCs and the consequent inhibition of the response mediated by effector T cells[22]. It has recently been shown in patients with metastatic non-small cell lung cancer that the TIM-3/Gal-9 pathway is directly involved in primary and secondary resistance to proven anti-PD1 immunotherapy[23].

Another molecule with potent inhibitory effects is SIRPα (signal-regulating protein alpha), which is considered an innate immune checkpoint, and it induces a "don't eat me" response[24]. It has been shown that SIRPα is expressed by MDSCs and that when it interacts with its CD47 ligand, a state of immunological tolerance to transplantation is induced. This phenomenon is attributed to the inhibition of the effector function of macrophages and dendritic cells mainly[25]. In an in vitro model of colorectal cancer and breast cancer, blockade of the SIRPα-CD47 interaction with tested monoclonals was shown to result in potentiation of the immune response, particularly the activation of monocytes, dendritic cells, and the effector functions of the T lymphocytes receptors[25].

Depletion of amino acids required by T cells

The arginase-1 enzyme is abundantly synthesized by MDSCs. This enzyme is responsible for transforming the amino acid L-arginine into L-ornithine and urea. This constant enzymatic reaction causes a deficiency of L-arginine in the tumor microenvironment. Deficient levels of this amino acid have a direct impact on the T

lymphocyte, since the L-arginine amino acids located in the zeta chain of CD3 are essential for the adequate transduction of the TCR signal, culminating in the suppression of the loss of the TCR. T lymphocytes[26].

Peripheral blood M-MDSC from patients with prostate cancer overexpress arginase-1. This finding has been associated with the progression of localized cancer to metastatic cancer. It is relevant that these results were obtained from the samples of patients with prostate cancer who received surgery or prostatectomy as treatment[27]. Another study identified that patients with pancreatic cancer had elevated levels of arginase-1 compared to the levels of healthy subjects. This increase in arginase-1 was attributed to the increase in circulating MDSC in peripheral blood[28].

Cysteine is another amino acid that reduces the presence of MDSCs. They internalize cystine from the extracellular medium into their cytoplasm for their conversion into cysteine, but they do not allow this amino acid to be exported, which in turn induces a cysteine deficiency in the microenvironment that has repercussions in emerging cells such as dendritic cells, macrophages, and especially T lymphocytes[29].

Production of reactive oxygen and nitrogen species

Another enzyme overexpressed by MDSCs is iNOS (inducible nitric oxide synthase), which is responsible for producing nitric oxide from L-arginine. Overexpression of the enzyme causes a higher concentration of nitric oxide (NO), and this in turn favors the production of reactive oxygen species (ROS) and nitrogen species (RNS) that interfere with multiple cellular processes, particularly interleukin-2 signaling, with its receptor and TCR alterations due to the process called nitration[30,31].

Adenosine and adenosine receptors

Large amounts of ATP, the molecule that is sequentially degraded to become adenosine, are concentrated in the microenvironment of hypoxic tumors. The process begins with the cleavage of ATP into ADP by the CD39 surface protein, then ADP is cleaved into adenosine by the CD73 protein[32,33]. These two clusters of differentiation (CD) are abundantly expressed on the cell membrane of MDSCs[34]. Adenosine in the extracellular medium can interact with its specific A1, A2A, A2B, and A3 receptors[35]. Activation of the A2A receptor potently inhibits the effector function of macrophages, dendritic cells, and T lymphocytes, thereby altering the antitumor immune response at multiple levels[34-36].

It has been shown that the CD73 molecule is overexpressed in PMN-MDSC and M-MDSC from patients with head and neck cancer[37], non-small cell lung cancer[38], and colorectal cancer[39]. In the context of prostate cancer and bladder cancer, cancer cells underexpress CD73[40,41]. However, the expression profile of CD73 on MDSCs in these cancers is unknown.

miRNAs

MicroRNAs (miRNAs) are non-coding ribonucleic acid oligonucleotides approximately 22 nucleotides in length. The function of these molecules is gene regulation at the post-transcriptional level. The regulation mechanism consists of the pairing of complementary nitrogenous bases between the miRNA and the messenger RNA (mRNA), which prevents the assembled ribosome from accessing the sequencing agent and initiating the translation of the mRNA into protein, thus regulating gene expression[42].

In cancer patients, some miRNAs are overexpressed, particularly miR-21 in the context of prostate cancer, which is related to resistance to castration and disease progression[43,44]. Other miRNAs, whose levels are elevated in patients with prostate cancer, and which are associated with metastatic disease and inhibition of cancer cell apoptosis, are miR-18a, miR-32, miR-106, miR-125b, miR-141, miR-221, miR-375, miR-650, and miR-4534[45]. Although multiple miRNAs associated with prostate cancer are known, it is unknown whether these regulatory RNAs are exclusively synthesized by tumor cells or come from another cell type. The participation of MDSCs as cells secreting miRNAs contained in exosomes was recently broken. Among the miRNAs involved are: miR-690, miR-155, miR-21a, miR-494, miR-146a, miR-9, and miR-126a, miR-98, among others. These miRNAs actively participate in processes such as the evasion of apoptosis in tumor cells, expansion and differentiation of MDSCs, induction of regulatory T lymphocytes, regulation of inflammation in the tumor microenvironment, and angiogenesis[46,47]. Circulating peripheral blood miRNAs can be used as biomarkers in the context of prostate cancer[48]. The feasibility of detecting miRNAs in biofluids other than blood, such as urine and bile, has also been evaluated. In particular, urine is a biofluid that can be easily obtained from patients, and the levels of miRNAs obtained are comparable to the levels obtained from peripheral blood[49].

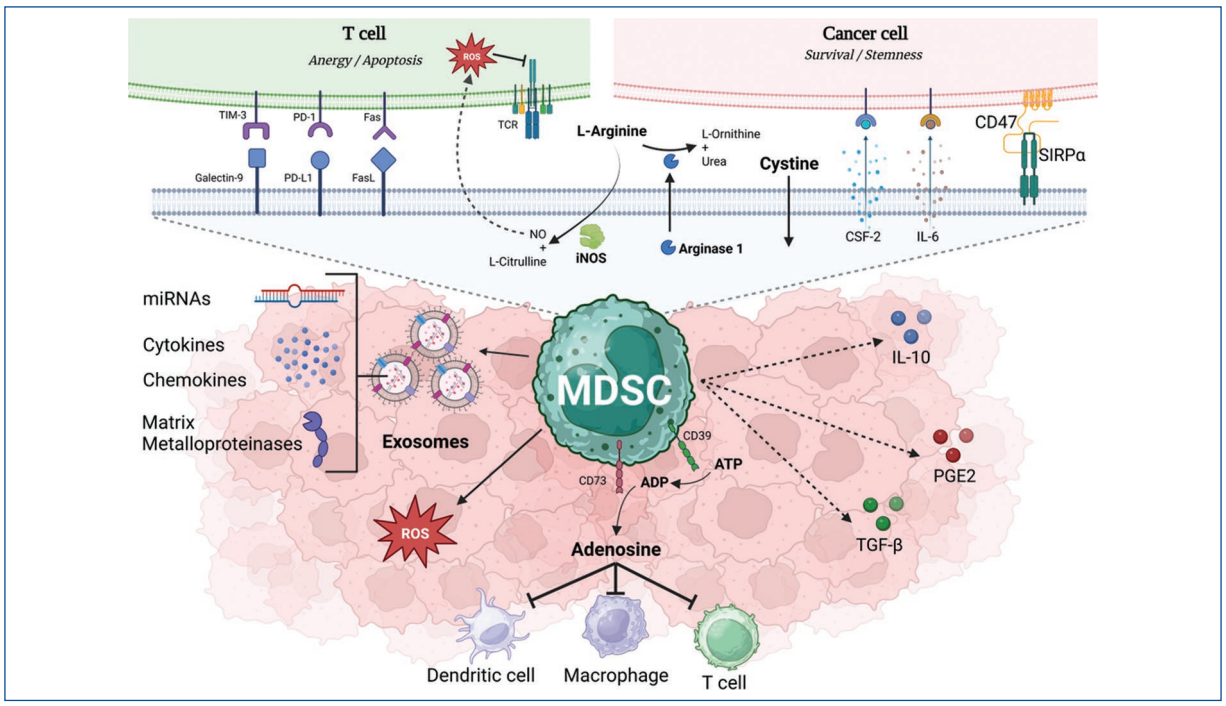

Figure 1. Immunosuppressive mechanisms used by suppressor cells of myeloid origin (MDSC) and their interaction in the tumor microenvironment; nitric oxide (NO), colony-stimulating factor 2 (CSF-2), prostaglandin E2 (PGE2), and reactive oxygen species (ROS).

However, factors that have a negative influence on the analysis of miRNAs in urine have been identified, such as hematuria, the method of obtaining it, and the intra-individual probability (different results in repeated measurements of the same subject). These factors are a limitation for the standardized analysis of miRNAs in urine[50]. It is currently unknown whether there are differences between the circulating miRNAs in patients with prostate cancer and candidates for different types of treatment (Fig. 1).

MDSC Regulations

The different therapeutic options used for the treatment of cancer such as chemotherapy, radiotherapy, and immunotherapy exert effects on tumor and non-tumor cells. MDSCs are a clear example of this. These cells respond variably to various stimuli[51,52].

In multiple studies, the effect produced by the administration of chemotherapy on the levels of MDSC present in patients with cancer models has been evaluated. Gemcitabine and 5-fluorouracil are agents that decrease MDSC both in animals and in cancer patients[52-54]. In the particular case of patients with cervical cancer, it has been observed that carboplatin and paclitaxel exert a favorable effect on the immune response by decreasing MDSC[53-55]. However, other chemotherapeutic agents such as doxorubicin and cyclophosphamide increase with reduced levels of MDSC[56]. Sunitinib is another drug used in the treatment of different types of cancer. The administration of sunitinib has been shown to decrease circulating MDSC in patients with renal cancer[57].

Radiotherapy is another frequently used therapeutic option. When administered, it induces immunostimulatory and immunosuppressive effects of which the recruitment and precursor of MDSC in the tumor are the immediate response of these cells to the damage induced by radiotherapy[51]. Local irradiation was shown to induce a marked intratumoral infiltration of MDSC in a mouse model of prostate cancer[58]. In contrast, in patients with hepatocellular carcinoma, the administration of radiotherapy resulted in a decrease in circulating MDSCs[59].

In the context of immunotherapy, MDSC exerts a predominant immunosuppressive effect. In vitro models have identified that the development of acquired resistance to immunotherapy is related to MDSC levels[60-62].

Other drugs and therapeutic alternatives also modulate MDSC. In 2020, Sieminska et al. evaluated the

circulating levels of MDSC in patients with prostate cancer who received different treatments. Among the most relevant findings, it was demonstrated that MDSC increased in quantity when patients received prostatectomy as the only treatment and that the increase is greater if the patient receives combination therapy[63]. Drugs used to treat conditions other than cancer directly influence MDSCs. Zoledronic acid, for example, alters the migration of these cells, and Vitamin A and Vitamin D influence their maturation and development process. Sildenafil alters their immunosuppressive function and celecoxib inhibits its expansion and immunosuppressive function[64-66]. Celecoxib is a COX-2-specific and commonly used non-steroidal anti-inflammatory drug. In addition to its anti-inflammatory activity, antitumor properties have been attributed to it[67,68]. This can be partly explained by the direct effect on MDSCs, which enhances the immune response[66,69,70].

Conclusion

MDSCs are cells that possess an extensive collection of immunosuppressive mechanisms that worsen the antitumor immune response. These cells arise as a physiological response to host damage but in the context of pathology such as cancer, and chronic infections, among others. The potent immunosuppressive effects that they exert result in exacerbated and non-physiological immunosuppression. Due to the multiple immunosuppressive mechanisms that they have, they constitute important target treatments, particularly in cancer, a condition in which they prominently favor the survival of cancer cells mainly through the evasion of the immune response. The role of MDSC in the cancer context is of primary importance due to the central position, it plays in the tumor microenvironment. Studying their interactions with cancer cells as well as cells of the immune system can answer the questions that remain about sustainable and effective changes in the treatment of prostate cancer, and the different mechanisms of resistance to treatment.

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Conflicts of interest

None.

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REVIEW ARTICLE

Perspectives of microRNAs in bladder cancer and their potential as biomarkers for the early diagnosis of the disease

Perspectivas de los microARN en el cáncer de vejiga y su potencial como biomarcadores para el diagnóstico precoz de la enfermedad

*Pedro Reyes-Martínez[1], Pablo C. Ortiz-Lazareno[2], Diana L. Cisneros-García[3], and Erick Sierra-Diaz[4]**

[1]Department of Physiology, Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara; [2]Division of Immunology, Centro de Investigación Biomédica de Occidente, Instituto Mexicano del Seguro Social (CIBO-IMSS); [3]Department of Public Health, Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara; [4]Division of Epidemiology, UMAE Hospital de Especialidades, Centro Médico Nacional de Occidente. Guadalajara. Jalisco, Mexico

Abstract

Bladder cancer is one of the most common malignant neoplasia. In 2020, the World Health Organization reported 573,278 cases and 212,536 deaths secondary to bladder cancer. The reported proportion of male and female is 4:1. As other malignant neoplasia, bladder cancer has shown that short molecules of non-coding ribonucleic acid, called microRNAs, play a regulatory role in the biological behavior of cancer cells and also in immune response cells. Around 2300 mature and functional miRNAs regulate gene expression post-transcriptionally by binding complementary bases to the messenger RNA sequence. This binding results in a decrease in messenger RNA translation and its subsequent degradation. There is also evidence that a specific microRNA can interact with various messenger RNA sequences, and conversely, a messenger RNA sequence can be the molecular target of multiple microRNAs. The aim of the present review is to show a general panorama of microRNAs role in bladder cancer cells.

Keywords: *Bladder cancer. miRNAs. RNA sequence. Messenger RNA. miRNAs biogenesis.*

Resumen

El cáncer de vejiga es una de las neoplasias malignas más comunes. En 2020 la Organización Mundial de la Salud reportó 573.278 casos nuevos y 212.536 muertes secundarias al cáncer de vejiga. La proporción hombre mujer reportada es de 4:1. Como en otras neoplasias malignas, en el cáncer de vejiga se ha demostrado que moléculas cortas de ácido ribonucleico no codificante, llamadas microARN, desempeñan un papel regulador en el comportamiento biológico de las células cancerosas y también en las células de respuesta inmune. Alrededor de 2.300 microARN maduros y funcionales que regulan la expresión génica postranscripcional uniendo bases complementarias a la secuencia del ARN mensajero. Esta unión da como resultado una disminución de la traducción del ARN mensajero y su posterior degradación. También hay evidencia de que un microARN específico puede interactuar con varias secuencias de ARN mensajero y, a la inversa, una secuencia de ARN mensajero puede ser el objetivo molecular de múltiples microARN. El objetivo de la presente revisión es mostrar el panorama general del papel de los microARN en las células de cáncer de vejiga.

Palabras clave: *Cáncer de vejiga. Micro ARN. Secuencia de ARN. RNA mensajero. Biogénesis de los miRNA.*

***Correspondence:**
Erick Sierra-Diaz
E-mail: erksland@gmail.com

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Introduction

Bladder cancer ranks as the seventh most common cancer in men, and when considering both sexes, it holds the eleventh position in incidence. In the year 2020, there were more than 573,278 new cases reported worldwide[1]. In Mexico, various types of genitourinary cancers account for 20% of all cancer types, and in 2012, bladder cancer constituted 2.2% of all registered tumors[2]. Regarding this neoplasm, approximately 75% are classified as non-muscle-invasive, while the remaining cases are present as a muscle-invasive disease at the time of diagnosis[3]. It is known that non-muscle-invasive bladder cancer represents a better prognosis and survival for patients; however, the disease often recurs. The most frequently observed symptoms in patients include painless hematuria, dysuria, increased frequency of urination, and urinary urgency[4]. Risk factors directly influencing bladder cancer development have been described, with modifiable factors including inadequate fluid intake, smoking, and exposure to compounds with aromatic amines. In contrast, non-modifiable risk factors include a family history of bladder cancer, male gender, being Caucasian 55 years or older, and chronic urinary tract infections[4].

Various malignancies have shown that short molecules of non-coding ribonucleic acid, called microRNAs (miRNAs), play a regulatory role in the biological behavior of cancer cells and also in immune response cells such as T lymphocytes, macrophages, dendritic cells, and NK cells[5-7]. MiRNAs are present in most bodily fluids[8-11]. In the context of bladder cancer, the presence of miRNAs in urine has been evaluated, and evidence indicates that there are differences in the miRNA profile in the urine of patients compared to that of healthy individuals[12,13].

Biogenesis of miRNAs

MiRNAs are non-coding ribonucleic acid molecules, with an approximate length of 21-23 nucleotides[14]. It is estimated that there are 2,300 mature and functional miRNAs[15] that regulate gene expression post-transcriptionally by binding complementary bases to the messenger RNA (mRNA) sequence. This binding results in a decrease in mRNA translation and its subsequent degradation[14]. There is also evidence that a specific miRNA can interact with various mRNA sequences, and conversely, a mRNA sequence can be the molecular target of multiple miRNAs[14].

Two pathways for miRNA synthesis have been described: the canonical pathway and the non-canonical pathway. The canonical pathway is the most studied, and it has been demonstrated that the majority of miRNAs are generated through this process[16]. The process begins when RNA polymerase II binds to deoxyribonucleic acid (DNA) and produces a transcript called pri-miRNA, which has a 7-methylguanosine cap at the 5' end and a continuous chain of adenine at the 3' end, known as a poly-A tail[16-18]. Subsequently, the pri-miRNA is enzymatically processed by the Drosha protein and the DGC8 protein [DiGeorge syndrome critical region [8], which together form a heterodimer called the microprocessor complex[17,18]. This protein complex cuts the ends of the pri-miRNA, resulting in a double-stranded ribonucleic acid (RNA) molecule through complementary base pairing into one portion, while the rest of its sequence forms an unpaired hairpin structure. This molecule is known as pre-miRNA[14,16].

The next step in pre-miRNA processing is its export from the cell nucleus to the cytoplasm, a task carried out by another essential heterodimer called the Exportin-5/RanGTPase complex[19]. In the cytoplasm, the pre-miRNA is enzymatically cleaved by the RNase III enzyme called Dicer, resulting in a double-stranded RNA molecule with free ends[20-22]. Finally, the RNA duplex is loaded onto proteins of the Argonaute family (Ago1-4) by the HSC70 and HSP90 chaperones through an adenosine triphosphate (ATP)-dependent process. The RNA duplex in the Ago protein is unwound to release the non-regulatory RNA strand, known as the passenger strand, while retaining the strand which is considered the true miRNA[20,23]. This ribonucleoprotein is known as the RNA-induced silencing complex (RISC) and represents the effector component of the canonical pathway for gene silencing and regulation at the mRNA level (Fig. 1)[22,24].

Perspective on miRNAs in the context of cancer

Evidence indicates that multiple miRNAs are dysregulated in most types of cancer[25]. Recent reports suggest that altered levels of miRNAs are directly related to tumor progression[26-28], evasion of the immune response[29,30], epigenetic reprogramming[31,32], and metastasis[33-34]. It has been demonstrated that tumor cells secrete a large number of exosomes loaded with various molecules, including miRNAs[36,37]. Furthermore,

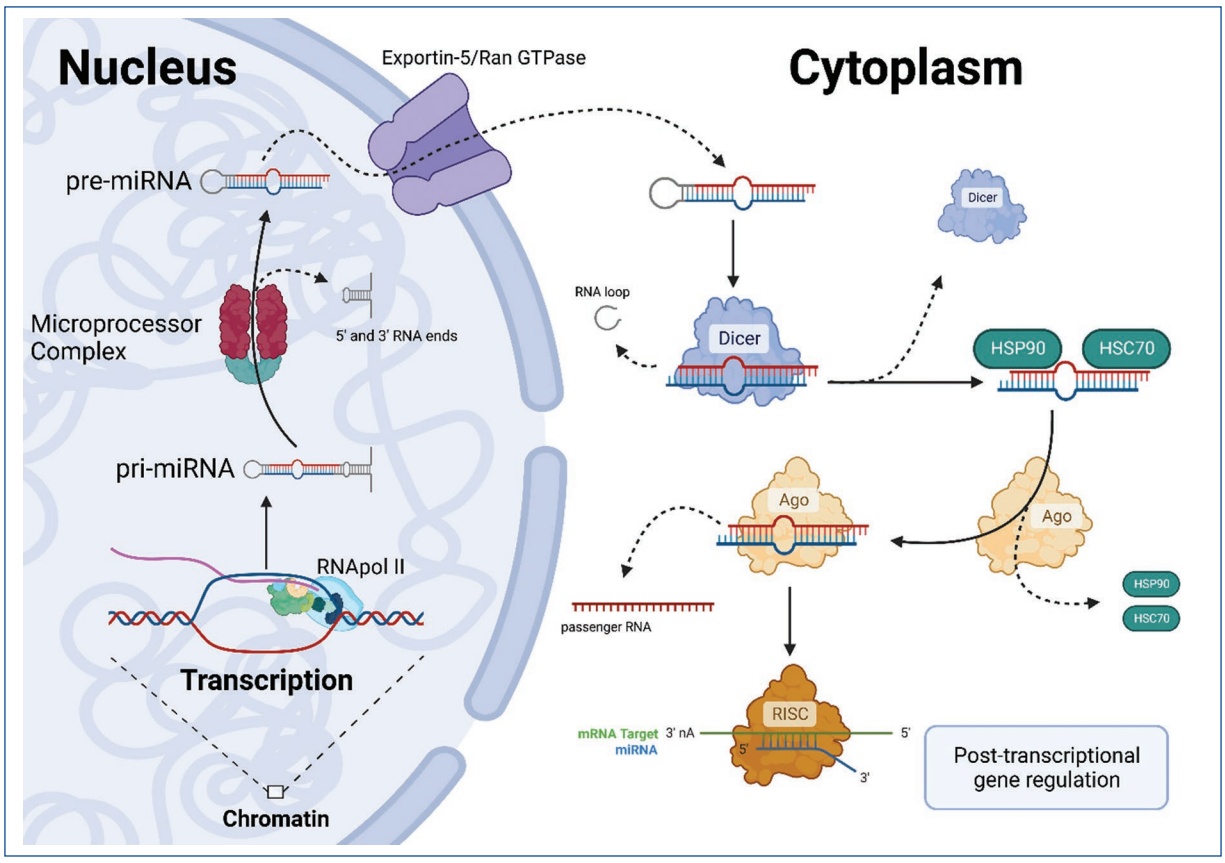

Figure 1. Canonical pathway for miRNA biogenesis. The transcription of chromatin is the first step of the pathway, further processing of the RNA molecule is mediated by two RNA endonucleases: Microprocessor Complex (two DGC8 proteins coupled to Drosha) and Dicer. In the cytoplasm, the proteins HSP90 and HSC70 guide the binding of pre-miRNA to Argonaute (Ago) protein. Finally, Argonaute discards the passenger RNA strand but retains the miRNA strand, this ribonucleoprotein is known as RNA-induced silencing complex (RISC). Created with BioRender.com.

it has been observed that the fusion of these exosomes with cells of the immune system, such as NK cells and cytotoxic T lymphocytes (CTLs), directly influences and suppresses the effector cytolytic activity of these cells[38,39]. This results in suboptimal immunosurveillance, favoring progression[40].

In the context of cancer, miRNAs can be classified according to the function attributed to them. Oncogenic miRNAs, or oncomiRs, are considered promoters of tumor development. MetastamiRs are considered enhancers of metastasis, and tumor suppressor miRNAs are attributed to the control and regulation of tumor proliferation[41-43]. Some years ago, another type of miRNA was described, called Epi-miRNAs. These have been studied in various pathologies, including cancer, and their attributed function is the regulation of cellular components, which are responsible for the epigenetic profile as well as the modulation of methylations in proteins and ribonucleic acid, known as epiproteome and epitranscriptome, respectively[44,45]. MiRNAs have also been identified that have a direct regulatory effect on cells of the innate and adaptive immune system, leading to their classification as immuno-miRs (Fig. 2)[29,46-56].

MiRNAs in bladder cancer

In the past decade, miRNAs have been extensively studied in patients with bladder cancer (Table 1). Some miRNAs have been proposed as potential diagnostic[57-59], prognostic[59-63], cancer recurrence, and chemotherapy resistance biomarkers[64,65]. Among the most studied, miRNAs in bladder cancer are miR-21, miR-30b, miR-141-3p, miR-143, miR-155, miR-200 family, miR-214, and miR-222[61,62,66-81]. In addition, miR-148a-3p and miR-152 have been identified as Epi-miRNAs

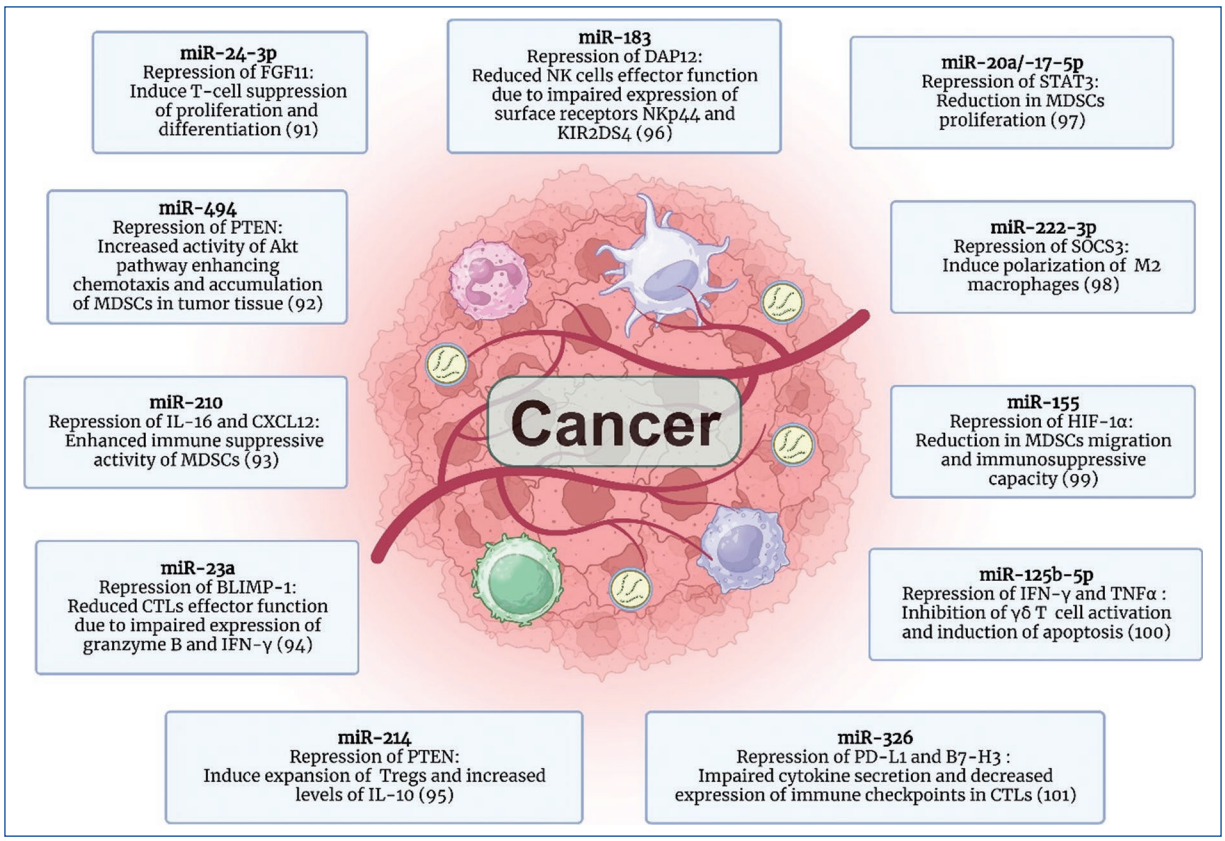

Figure 2. Immuno-miRs are involved in the process of immunosurveillance. Many miRNAs have been identified as potent modulators of proliferation, differentiation, and effector function of immune cells (Immuno-miRs). NK cells and cytotoxic T lymphocytes (CTLs) are the main cells responsible for immunosurveillance due to their cytolytic properties; some miRNAs negatively regulate their function. Myeloid-derived suppressor cells (MDSCs) and regulatory T lymphocytes (Tregs) are cells with extreme immunosuppressive capacity that contributes to tumor growth and immune escape. Some miRNAs directly influence the immunosuppressive function and expansion of these cells. Adapted from46-56.

because their molecular target is the mRNA of the gene encoding the DNMT1 protein (DNA methyltransferase 1), which regulates DNA cytosine methylation[82]. In patients with bladder cancer, decreased levels of these Epi-miRNAs in tumor tissue have been shown to be associated with increased proliferation of cancer cells[83,84].

MicroRNAs in urine: a source of non-invasive biomarkers

It has been demonstrated that miRNAs are present in a variety of bodily fluids, including serum, plasma, saliva, and urine (Table 2)[85-87]. Despite miRNAs being more stable and having a longer half-life than mRNA[79], comparative studies have been conducted to assess the efficiency of different kits and protocols available for purifying and isolating miRNAs with the greatest precision possible[86,87]. In bladder cancer, the profile of miRNAs has been analyzed and compared in different types of biological samples, such as plasma, serum, urine, exosomes in urine, exosomes in plasma, and PBMCs[85,88,89]. Although the miRNA profile has been evaluated in various biofluids and proposed as diagnostic biomarkers[89-92], there is no consensus on the specific miRNAs that should be evaluated.

miRNAs in urine, specifically in exosomes present in urine, correlate with the miRNA profile in tumor tissue, particularly in patients with bladder cancer[85]. Compared to tissue biopsy, urine is a non-invasive and relatively simple sample to obtain, either through transurethral urinary catheterization or voluntary patient urination. Clinicians can obtain a biological sample that can

Table 1. Dysregulation of key miRNAs in patients with bladder cancer

miRNA	mRNA Target	Description	Reference
miR-21 ↑	PTEN	Inhibition of tumor suppressor PTEN leads to cancer progression and recurrence	58,59
miR-30b ↓	N/A	Potential classifier of invasive and non-invasive bladder cancer.	57,60,64
miR-141-3p ↑	AUF1	Inhibition of AUF1 results in greater proliferative capacity of bladder cancer cells. Overexpression of miR-141-3p is associated with poor prognosis.	61-63
miR-143 ↓	AKT, ERK5, RAS	Tumor suppressor effects, down-regulation of miR-143 leads to proliferation and tumor growth.	65,66
miR-155 ↑	DMTF1	Inhibition of DMTF1 promotes cancer growth. High expression is correlated with poor prognosis.	67,68
miR-200a/b/c ↑	ZEB1/2	Inhibition of ZEB1/2 prevents cancer cells from undergoing epithelial-mesenchymal transition, thus acting as a tumor suppressor. As the tumor progresses, the expression levels of the miR-200 family decrease.	69
miR-214 ↓	Netrin-1	Tumor suppressor effect, promoting apoptosis through regulation of Akt signaling	70
miR-222 ↑	PPP2R2A	High levels of miR-222 are directly related to cancer progression. Inhibition of PPP2R2A expression by miR-222 leads to activation of Akt/mTOR axis.	71,72

Arrows indicate high expression (↑) and low expression (↓). N/A, no evidence found in bladder cancer patients.

Table 2. miRNA profile in different samples from patients with bladder cancer

Sample	miRNAs profile	Reference
Plasma	miR-541, miR-200b, miR-566, miR-487, miR-148b	81
Plasma exosomes	miR-451a, miR-16-5p, miR-223-3p, miR-548ai, miR-548aa, miR-378e, miR-338-3p	76
Serum	miR-451a, miR-381-3p, miR-223-3p, miR-142-5p, miR-27b-3	80
Urine	miR-31-5p, miR-93-5p, miR-191-5p	85
Urine exosomes	miR-26a, miR-93, miR-191, miR-940	83
PBMCs	miR-451a, miR-16-5p, miR-144-3p, let-7a-5p, miR-15b-5p, miR-223-3p, let-7b-5p	76
Tumor	miR-4454, miR-720, let-7a-5p, miR-205-5p, miR-145-5p, miR-200c-3p	76

provide valuable information if processed appropriately and targeted[85-92]. Urine analysis in this neoplasm is of relevance as it reflects, to some extent, what is happening in the tumor microenvironment[93].

Conclusion

miRNAs are a significant focus of study today, given their role in regulating a wide range of cellular processes, particularly in the context of malignant neoplasms. Cystoscopy remains the preferred method for diagnosing bladder cancer[94,95], being a relatively straightforward procedure conducted by trained medical personnel. However, recent evidence suggests that cystoscopy has notable limitations in detecting early-stage pT0 bladder cancer[96], causing pain and anxiety in patients[97,98]. Therefore, it is crucial to develop complementary or alternative diagnostic tools that can identify the malignant condition in its early stages. MiRNAs are molecules that are tightly regulated[99], and alterations in their expression levels indicate disruptions in cellular physiology. Whether they increase or decrease, their dysregulation affects multiple cellular pathways, as most miRNAs have an affinity for different mRNAs.

The early identification of a dysregulated miRNA profile could be the initial step in a comprehensive approach to asymptomatic bladder cancer patients, where the procedure would be painless due to easy sample acquisition. Several miRNAs have been proposed as diagnostic and prognostic biomarkers in bladder cancer, although the specific miRNAs for this pathology have not been precisely described. Therefore, more research is needed to obtain

compelling evidence that enables the establishment of a consensus for the targeted analysis of specific miRNAs.

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Conflicts of interest

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Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

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CASO CLÍNICO

Uropatía obstructiva como presentación clínica inicial de sarcoidosis: reporte de caso y revisión de literatura

Urinary obstruction as the initial clinical presentation of sarcoidosis: a case report and the review of the literature

Jorge D. Rodríguez-Ferreyra, Pedro Ávila-Herrera y Rodrigo García-Urbina*

Hospital General, Centro Médico Nacional La Raza, Ciudad de México, México

Resumen

La sarcoidosis es una enfermedad multisistémica de causa desconocida, comúnmente afecta a jóvenes y adultos de edad media. Con frecuencia se presenta con adenopatía hiliar bilateral, infiltración pulmonar y lesiones cutáneas; pueden estar afectados el hígado, el bazo, los ganglios linfáticos, el corazón, el sistema nervioso central y el hueso. Varón de 41 años el cual inicia su cuadro clínico con cólico renoureteral, al realizar protocolo de estudio se diagnostica por medio de TAC litiasis renal y ureteral bilateral, sin embargo, durante la inspección destaca la adenopatía por lo que se realiza biopsia de ganglio inguinal en donde se diagnostica sarcoidosis. En la mayor parte de los casos, el diagnóstico de sarcoidosis es por exclusión, ya que sus manifestaciones clínicas son variadas. Estas consisten en patrones obstructivos o restrictivos de la vía aérea, uveítis y lesiones cutáneas. Los síntomas urinarios como presentación clínica inicial son raros.

Palabras clave: *Uropatía obstructiva. Sarcoidosis.*

Abstract

Sarcoidosis is a multisystemic disease of unknown cause, commonly affecting young and middle-aged adults. It frequently presents with bilateral hilar adenopathy, pulmonary infiltration, and skin lesions; the liver, spleen, lymph nodes, heart, central nervous system, and bone may be affected. A 41-year-old male who began with renal colic, when carrying out the protocol, is diagnosed through CT scan bilateral renal and ureteral lithiasis, however, during the inspection, the lymphadenopathy was highlighted, for which a biopsy was performed in the inguinal node where sarcoidosis is diagnosed. The diagnosis of sarcoidosis, in most of the cases, is given by exclusion because the clinical manifestations are varied. They consist of obstructive or restrictive airway patterns, uveitis, and skin injuries. Urinary symptoms as the initial clinical presentation are rare or unusual.

Keywords: *Urinary obstruction. Sarcoidosis.*

***Correspondencia:**
Jorge D. Rodríguez-Ferreyra
E-mail: daniel_rf_94@hotmail.com

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Introducción

Históricamente la sarcoidosis fue descrita en 1877 por el dermatólogo inglés J. Hutchinson; el caso presentado en su tiempo fue llamado «psoriasis papilar». En 1924 se acuñó por primera vez el término de «sarcoidosis» o «linfogranulomatosis benigna»[1].

Definida por la American Thoracic Society y la European Respiratory Society como una enfermedad multisistémica de causa desconocida, comúnmente afecta a jóvenes y adultos de edad media. Con frecuencia se presenta con adenopatía hiliar bilateral, infiltración pulmonar y lesiones cutáneas; pueden estar afectados el hígado, el bazo, los ganglios linfáticos, el corazón, el sistema nervioso central y el hueso.

Su etiología aún es desconocida, aunque se han estudiado factores genéticos relacionados con el antígeno leucocitario humano, así como su asociación con agentes antigénicos como bacterias, virus o retrovirus, o con agentes ambientales que activan una respuesta inmunitaria por parte de los linfocitos y de los macrófagos. Se presume que el inicio de la enfermedad ocurre en los pulmones, por lo que su asociación con agentes ambientales inhalados aumenta la sospecha; sin embargo, la respuesta inmunitaria persistente y sistémica aún es motivo de estudio[1].

El diagnóstico por lo regular es de exclusión de otras patologías; la clínica dependerá de los órganos afectados en cada paciente. El estudio de histopatología confirma la sospecha[1,2].

La afección endocrina en la sarcoidosis obedece principalmente a la hipercalcemia, que se presenta en el 5-10% de los pacientes; la hipercalciuria es más frecuente, cerca de tres veces más. Su fisiopatología se basa en que los macrófagos dentro del granuloma producen 25-hidroxicolecalciferol que posteriormente se convierte a 1-25-colecalciferol, activando así la vitamina D, lo cual da como resultado hipercalcemia, formación de litos en la vía urinaria y falla renal[1,3].

Las alteraciones endocrinológicas, aunado con la predisposición a litiasis que se pueden desencadenar debido a esta patología, han sido poco estudiadas, pero pueden impactar de forma importante en la función renal[1].

Caso clínico

Varón de 41 años, originario de Pachuca Hidalgo, previamente sano, niega patología crónica degenerativa, niega antecedentes quirúrgicos previos. Inicia el padecimiento actual con presencia de dolor abdominal localizado en el flanco derecho, el cual se irradia a la región genital, de intensidad 8/10 en la escala visual análoga del dolor, acompañado de náusea y vómito en dos ocasiones.

Acude a urgencias en nuestra unidad y se da sospecha inicial de cólico renoureteral, por lo que se solicitan estudios de extensión. La tomografía computarizada (TC) simple abdominopélvica muestra litiasis ureteral bilateral y litiasis renal bilateral.

Es valorado por el servicio de urología, donde en la exploración física destacan adenopatías supraclaviculares bilaterales de aproximadamente 1 cm, móviles, no dolorosas; y adenopatías submaxilares y retroauriculares, e inguinales, de hasta 2 cm, móviles, sin dolor a la palpación.

Laboratorios: urea 50, creatinina 2.7, sin reacción leucocitaria, electrolitos y tiempos de coagulación dentro de parámetros normales.

De acuerdo con los hallazgos de la TC, previo protocolo, con prueba rápida de SARS-CoV-2 negativa, se realiza cirugía con ureterolitotricia láser más colocación de catéter JJ bilateral. El procedimiento transcurre sin complicaciones. Una vez resuelta la urgencia, se inicia protocolo de estudio ante los hallazgos de la exploración física. Se analiza la TC previa (Figs. 1 y 2).

Se sospechan de forma inicial procesos infecciosos, como virus de la inmunodeficiencia humana (VIH) o tuberculosis miliar, por lo que se solicitan las siguientes determinaciones: hepatitis C 0.04 COI, HBsAg 0.17 s/co, aHBc 0.13 s/co, VIH 0.08 s/co, tinción de Ziehl-Neelsen negativa, reacción en cadena de la polimerasa para SARS-CoV-2 negativa. Tras la valoración por el servicio de infectología se descarta la sospecha inicial. Los marcadores tumorales son negativos: AFP 1.37 ng/dl, HCG < 0.10 MUI/ml, CA-19 95.05 U/ml.

Posterior a la resolución quirúrgica inicial de urgencia se decide el abordaje de la litiasis renal, por lo que se realiza nefrolitotricia con láser flexible derecha más retiro y colocación de catéter JJ derecho, y toma de biopsia escisional de ganglio inguinal derecho.

Se realiza un último abordaje quirúrgico para la resolución de la litiasis renal, con nefrolitotricia con láser flexible izquierda, más retiro de catéter JJ bilateral, y el paciente queda libre de litos.

Se remite a valoración por hematología ante la sospecha de linfoma, donde contemplan dicha posibilidad en espera del resultado de histopatología del ganglio inguinal y realizan seguimiento por su parte. El resultado de patología que se muestra en la figura 3, es sugestivo a etiología de origen auto inmune. Debido al diagnóstico sugestivo es valorado por reumatología, donde se confirma el diagnóstico de sarcoidosis y se inicia tratamiento con corticoesteroide y seguimiento en consulta externa.

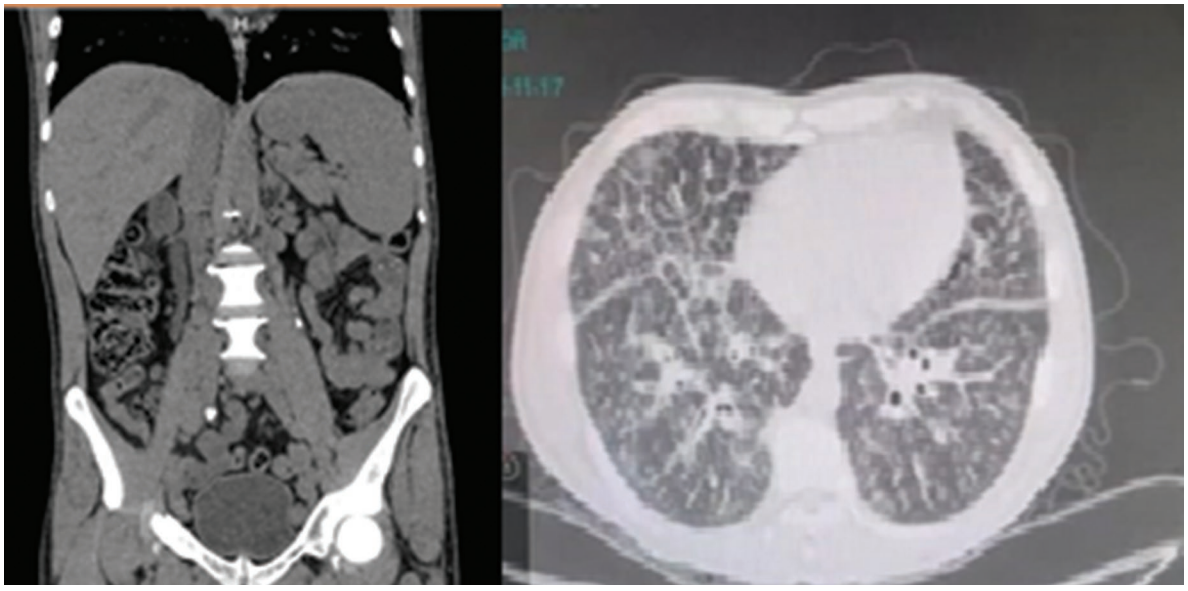

Figura 1. Tomografía computarizada simple. A la izquierda, corte coronal, en el cual se evidencia litiasis ureteral bilateral. A la derecha, corte axial de tórax que muestra infiltrados bilaterales, reportados como fibrosis.

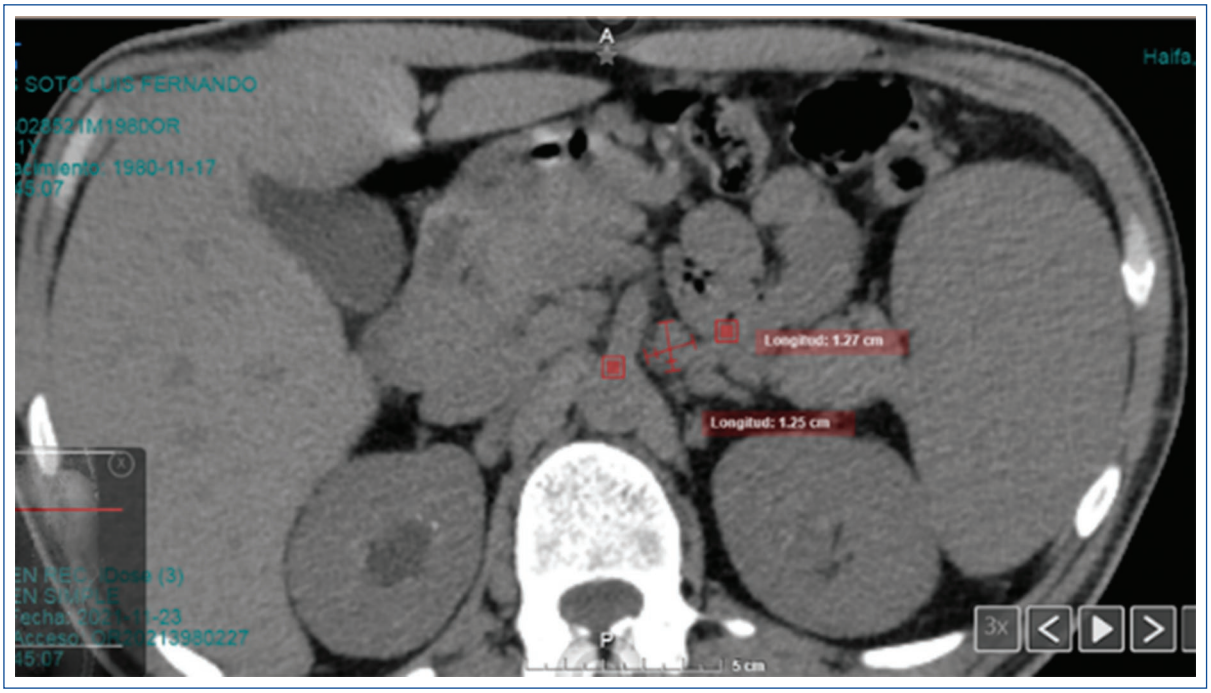

Figura 2. Tomografía computarizada simple, corte axial, en el cual se observa una adenopatía paraaórtica de 12.7 × 12.5 mm, regular y homogénea, sin calcificaciones en su interior.

El paciente se encuentra en seguimiento por reumatología y urología en consulta externa, con función renal reportada con urea 92 mg/dl y creatinina 2.5 mg/dl. Enviado a nefrología, continúa con tratamiento corticoesteroide. El pronóstico es dependiente de la respuesta al tratamiento otorgado por reumatología, mismo que se dicta por función pulmonar y función renal.

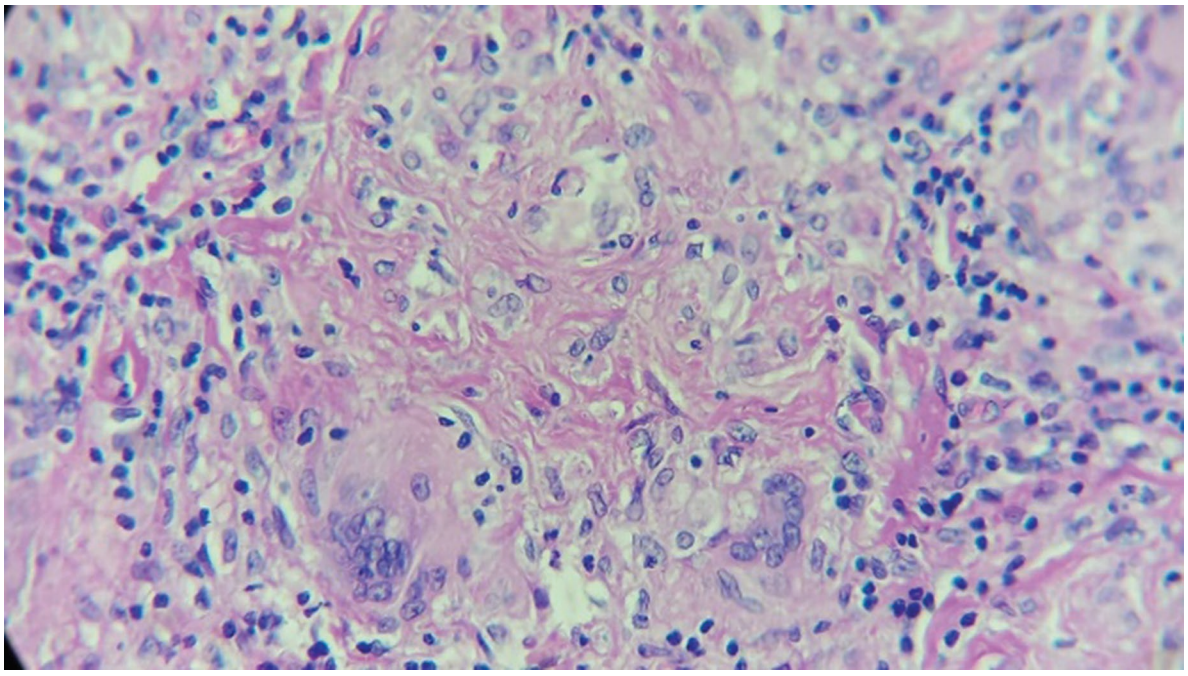

Figura 3. Corte histológico con tinción de hematoxilina y eosina en el que se observan zonas características de granulomas, en cuyo centro se encuentran células epiteliales, zonas bien circunscritas de reacción inflamatoria.

Discusión

La sarcoidosis es una enfermedad con poca incidencia en personas latinas y su presentación clínica más común es con alteración restrictiva u obstructiva de vía aérea, lesiones cutáneas y uveítis.

La presentación de nefrolitiasis como síntoma inicial es rara, aunque existe una incidencia del 7-12% de sarcoidosis y alta carga litiásica. Su fisiopatología se relaciona con el metabolismo de la vitamina D y en los estudios se han relacionado la presencia de nefropatía intrínseca por sarcoidosis y la formación de litos en la vía urinaria.

La importancia del caso radica en la baja incidencia en nuestro medio, el comportamiento de la enfermedad como diagnóstico de exclusión y que se presentó como síntoma inicial alta carga litiásica, con hallazgo de adenopatías. El inicio de un protocolo de estudio es importante, pues el diagnóstico oportuno impacta en la esperanza de vida.

Financiamiento

Ninguno.

Conflicto de intereses

Los autores declaran que no existen conflicto de intereses.

Responsabilidades éticas

Protección de personas y animales. Los autores declaran que los procedimientos seguidos se conformaron a las normas éticas del comité de experimentación humana responsable y de acuerdo con la Asociación Médica Mundial y la Declaración de Helsinki.

Confidencialidad de los datos. Los autores declaran que han seguido los protocolos de su centro de trabajo sobre la publicación de datos de pacientes.

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PERMANYER

CASO CLÍNICO

Ureteritis quística. ¿Qué tan frecuente es?

Cystic ureteritis. How prevalent is it?

María R. Ramírez-Solorio[1], Sandra X. Cruz-Ordóñez[2], José A. Aguilar-Villavicencio[1,2] y Fausto A. García-Trejo[2]*

[1]Servicio de Urología, Hospital Regional 1.º de Octubre, Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado; [2]Servicio de Urología, Hospital Azura Centro. Ciudad de México, México

Resumen

La ureteritis quística fue reportada por primera vez por Morgagni en el siglo XVIII. Los primeros en describirla fueron Richmond y Robb, como un proliferación caracterizada por múltiples quistes y defectos de limadura en el urotelio. Radiográficamente, la apariencia es la de múltiples quistes pequeños de 2 a 5 mm, defectos de obturación lisos, amurallados, redondeados y transparentes que se proyectan en la luz del uréter. Es una rara condición benigna que afecta al uréter y la pelvis renal. Características que se presentaron en la paciente que mostramos en este caso clínico. Mujer de 73 años con antecedentes de diabetes mellitus, hipertensión arterial sistémica e insuficiencia cardiaca. Ingresó por un cuadro de infección urinaria de repetición. Al realizar el abordaje diagnóstico se evidencia litiasis renal derecha y pielonefritis enfisematosa HUANG II. Se colocó catéter doble J derecho y se pautó antibiótico parenteral. Al momento de resolverse la litiasis urinaria se evidenció la presencia de ureteritis quística en el tercio medio y superior del uréter derecho. La ureteritis quística es muy rara y suele diagnosticarse incidentalmente mientras se busca otra patología. Se ha planteado que la causa es una respuesta inflamatoria crónica secundaria a una irritación recurrente de la mucosa de los uréteres, como puede ser el caso de la paciente en estudio.

Palabras clave: *Ureteritis. Infección. Litiasis.*

Abstract

Cystic ureteritis was first reported by Morgagni in the 18th century. The first to describe it were Richmond and Robb, as a flourishing characterized by multiple cysts and filing defects in the urothelium. Radiographically, the appearance is that of small multiple cysts of 2 to 5 mm, smooth, walled, rounded and transparent obturation defects that project into the lumen of the ureter. Is a rare benign condition that affects the ureter and renal pelvis. Characteristics that occur in the patient that we show in this clinical case. A 73-year-old woman with a history of diabetes mellitus, systemic arterial hypertension and heart failure. She was admitted due to recurrent urinary tract infection. When performing the diagnostic approach, right renal lithiasis and HUANG II emphysematous pyelonephritis were evidenced, placing a right double J catheter and parenteral antibiotic. When the urinary lithiasis was resolved, the presence of cystic ureteritis in the middle and upper third of the right ureter was evident. Cystic ureteritis is usually very rare, being diagnosed incidentally while searching for another pathology. It has been hypothesized that the cause is the chronic inflammatory response secondary to a recurrent recurrence of the ureteral mucosa, as may be the case of the patient under study.

Keywords: *Ureteritis. Infection. Lithiasis.*

***Correspondencia:**
María R. Ramírez-Solorio
E-mail: mrramirez0110@gmail.com

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Introducción

La ureteritis quística fue reportada por primera vez por Morgagni en el siglo XVIII. Los primeros en describirla fueron Richmond y Robb, como una proliferación caracterizada por múltiples quistes y defectos de limadura en el urotelio[1]. Se ha planteado la hipótesis de que la causa es la respuesta inflamatoria crónica secundaria a una irritación recurrente de la mucosa de los uréteres[2]. El diagnóstico puede hacerse radiográficamente o endoscópicamente, y la biopsia en general no es necesaria[3]. Suele tener la apariencia de múltiples quistes pequeños, de 2 a 5 mm, redondeados y transparentes, que se proyectan en la luz del uréter[1].

El tratamiento de la ureteritis quística tiene como objetivo el alivio de los síntomas, así como de la obstrucción. La resección ureteroscópica con electrocauterio de asa o ablación con láser es segura y bien tolerada, con resultados aceptables en los pacientes afectados, al igual que otras modalidades de tratamiento endoscópico para los pacientes con obstrucción, que incluyen la dilatación con balón, la instilación de nitrato de plata y la terapia antibiótica con un éxito variable a largo plazo[2].

El pronóstico se considera favorable, la obstrucción del tracto urinario superior es extremadamente rara y no se han reportado muertes por esta patología.

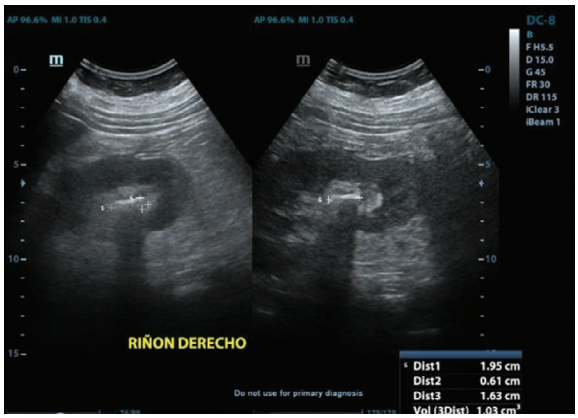

Figura 1. Ultrasonido renal con presencia de lito renal derecho de 1 cm.

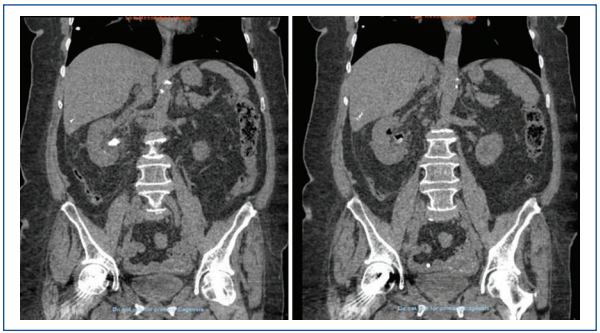

Figura 2. Tomografía simple de abdomen y pelvis en corte coronal con presencia de litos y gas en riñón derecho.

Caso clínico

Mujer de 73 años con antecedentes de diabetes *mellitus* e hipertensión arterial sistémica, que ingresó por un cuadro de infección urinaria recurrente. Al realizar el abordaje diagnóstico se evidencia litiasis renal derecha por ultrasonido (Fig. 1). Se solicita tomografía computarizada simple de abdomen (Fig. 2), que muestra pielonefritis enfisematosa derecha HUANG II, litos de 10 mm, uno en el cáliz renal y el segundo en la pelvis renal, y lesión de aspecto quístico derecho de 10 mm. Laboratorios: leucocitos 16,000, neutrófilos 84%, hemoglobina 13.6 g/dl, hematocrito 40%, plaquetas 478,000, glucosa 113 mg/dl, urea 47 mg/dl, creatinina 1.1 mg/dl. Examen general de orina: glucosa 500 mg/dl, proteínas 100 mg/dl, esterasa leucocitaria 70, leucocitos incontables, bacterias abundantes, eritrocitos 6-8 por campo.

Se indica colocación de catéter doble J derecho y antibioticoterapia con carbapenémico. La urotomografía de control sin evidencia de gas. Se indica tratamiento quirúrgico.

Al realizar la ureteroscopia derecha se observan múltiples lesiones quísticas en el tercio medio y superior del uréter (Fig. 3). Se realiza litotricia con láser, fragmentando el lito de pelvis en su totalidad. Se coloca un catéter doble J y se cumple con esquema de antibiótico. En un segundo tiempo quirúrgico, al realizar la ureteroscopia se observa persistencia de lesiones quísticas en el uréter y se resuelve el lito en el cáliz renal inferior en su totalidad. Es egresada sin complicaciones, para posterior retiro del catéter doble J.

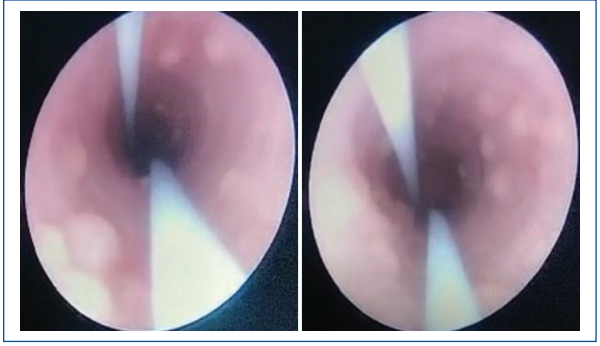

Figura 3. Visión endoscopia de uréter derecho con presencia de múltiples quistes en luz ureteral.

Conclusiones

La ureteritis quística es una rara condición benigna que afecta al uréter y la pelvis renal. La localización más frecuente de las lesiones quísticas es el uréter proximal, pero se pueden encontrar a cualquier nivel del urotelio[1]. La clínica es inespecífica y se pueden presentar cuadros de hematuria microscópica o macroscópica, cólico nefrítico o infección urinaria, como en la paciente del caso, que ingresó por un cuadro de infección urinaria secundario a litiasis renal.

El diagnóstico de ureteritis es por exclusión y se basa en la exploración urográfica y endoscópica. En esta paciente se confirmó la afectación del uréter medio y proximal durante la ureteroscopia, ya que al realizar la tomografía computarizada no se observaron defectos de llenado que nos indicaran sospecha de lesiones quísticas, y el diagnóstico de uretritis quística fue un hallazgo incidental al momento de resolver el cuadro litiásico.

La uretritis quística se asocia con irritación urotelial crónica que puede ser causada por nefrolitiasis e infecciones del tracto urinario, como fue en nuestro caso. Sin embargo, no existen guías para el manejo de la ureteritis quística, además del tratamiento de la causa subyacente. Dependiendo de la literatura base, se puede ofrecer solo tratamiento antibiótico o tratamiento quirúrgico en casos de quistes de gran tamaño para resolver el cuadro de obstrucción, que va desde la colocación de un catéter doble J, la resección ureteroscópica con electrocauterio de asa o ablación con láser y hasta llegar a extremos de realizar una nefroureterectomía radical o una ureterectomía segmentaria si se sospecha neoplasia del tracto urinario superior tras un examen diagnóstico exhaustivo o por la persistencia de síntomas infecciosos u obstructivos, y una toma de muestras de tejido[2].

La ureteritis quística debe considerarse como diagnóstico diferencial en caso de hallazgos radiológicos atípicos. Si el paciente se encuentra asintomático, no requerirá tratamiento invasivo. Se recomienda el seguimiento semestral con análisis de orina, citología, urocultivo y estudio urográfico.

En el contexto actual se reportan solo unos cientos de informes en la literatura, siendo desconocida la prevalencia de la ureteritis quística, por lo cual es de gran importancia que se reporten los casos que se producen alrededor del mundo en los diferentes centros hospitalarios para evaluar la prevalencia y la conducta diagnóstica y terapéutica, ya que con ello se podrán unificar criterios y dar mejor tratamiento a los pacientes.

Agradecimientos

Los autores agradecen a todas las personas involucradas para llevar a cabo este artículo.

Financiamiento

Los autores no recibieron patrocinio para llevar a cabo este artículo.

Conflicto de intereses

Los autores declaran no tener ningún conflicto de intereses.

Responsabilidades éticas

Protección de personas y animales. Los autores declaran que los procedimientos seguidos se conformaron a las normas éticas del comité de experimentación humana responsable y de acuerdo con la Asociación Médica Mundial y la Declaración de Helsinki.

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CASO CLÍNICO

Malacoplaquia vesical e hidronefrosis bilateral: reporte de un caso

Bladder malacoplakia and bilateral hydronephrosis: a case report

Israel Arellano-Romero, Gerardo Moreno-Pérez, Juan P. Landaverde-Sandoval, Eduardo Guzmán-Emiliano y Roberto E. Chapa-Abrego*

Departamento Institucional Adscrito, Servicio de Urología, Hospital Regional ISSSTE, Benemérita Universidad Autónoma de Puebla, Puebla, Pue., México

Resumen

La malacoplaquia es una enfermedad granulomatosa crónica asociada a inmunosupresión e infección que afecta principalmente a la vejiga. Se caracteriza por la presencia de nódulos, placas o úlceras en la vejiga, síntomas del tracto urinario inferior y hematuria. Puede mimetizar el cuadro clínico del cáncer vesical. Se presenta el caso de una paciente de 66 años con hematuria y síntomas del tracto urinario inferior. Inicialmente se diagnosticó carcinoma urotelial de alto grado, pero tras una revisión histopatológica se confirmó el diagnóstico de malacoplaquia. Se inició tratamiento médico y actualmente el cuadro se encuentra en remisión. La malacoplaquia es una enfermedad extremadamente rara que debe considerarse en pacientes con infecciones urinarias recurrentes y hallazgos tumorales en la cistoscopia, ya que puede ser confundida con cáncer vesical. El diagnóstico y tratamiento temprano son importantes para evitar intervenciones quirúrgicas innecesarias y complicaciones asociadas.

Palabras clave: *Malacoplaquia. Cáncer vesical. Hidronefrosis bilateral. Hematuria. Reporte de caso.*

Abstract

Malacoplakia is a chronic granulomatous disease associated with immunosuppression and infection that mainly affects the bladder. It is characterized by the presence of nodules, plaques or ulcers in the bladder, lower urinary tract symptoms and hematuria. It can mimic the clinical picture of bladder cancer. The case of a 66-year-old female patient with hematuria and lower urinary tract symptoms is presented. Initially, high-grade urothelial carcinoma was diagnosed, but after histopathological review, the diagnosis of malacoplakia was confirmed. Medical treatment was started, and the condition is currently in remission. Malacoplakia is an extremely rare disease that should be considered in patients with recurrent urinary tract infections and tumor findings on cystoscopy, since it can be confused with bladder cancer. Early diagnosis and treatment are important to avoid unnecessary surgical interventions and associated complications.

Keywords: *Malakoplakia. Bladder cancer. Bilateral hydronephrosis. Hematuria. Case report.*

***Correspondencia:**
Juan P. Landaverde-Sandoval
E-mail: jplandaverde@gmail.com

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Introducción

La malacoplaquia es una enfermedad granulomatosa crónica que afecta principalmente a la vejiga, caracterizada por la presencia de nódulos, placas o úlceras. Se debe a un defecto en el sistema fagocitario bacteriano y está relacionada con inmunocompromiso e infecciones del tracto urinario inferior, especialmente por *Escherichia coli*. Es una condición extremadamente rara, con un pico de incidencia alrededor de los 50 años y más común en mujeres. El diagnóstico se hace por medio de histopatología, identificando histiocitos largos (células de von Hansemann) y esférulas basófilas (cuerpos de Michaelis-Gutmann). El tratamiento se centra en el control de infecciones con antimicrobianos, incluyendo sulfonamidas, rifampicina y fluoroquinolonas. Algunos compuestos como el ácido ascórbico y el betanecol también pueden mejorar la función fagocítica de los macrófagos[1]. Dada su rareza, es esencial aumentar la conciencia y el conocimiento para mejorar la detección y el manejo de la malacoplaquia.

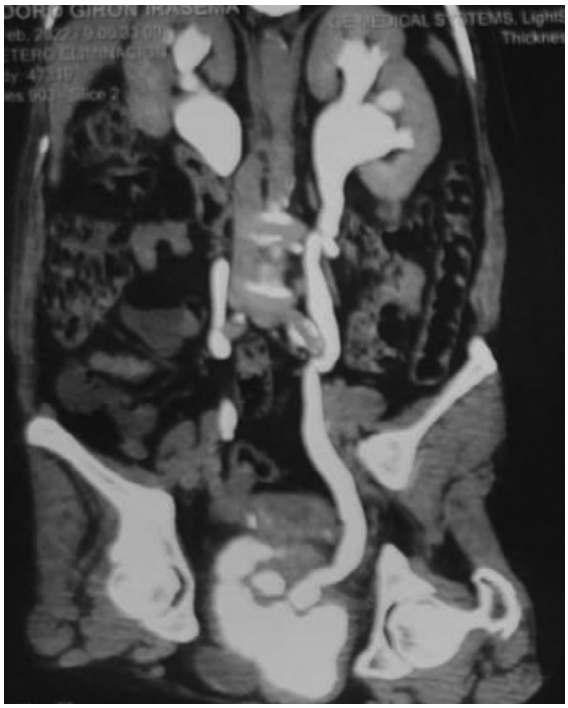

Figura 1. Tomografía contrastada fase excretora.

Caso clínico

Paciente de sexo femenino de 66 años con antecedente de diabetes *mellitus* tipo 2 diagnosticada en 2012 en tratamiento con hipoglucemiantes orales. Inicia padecimiento actual con infecciones del tracto urinario de repetición en tres ocasiones corroboradas por urocultivo, recibiendo tratamiento no especificado. Posteriores a estas se presenta cuadro hematuria macroscópica, razón por la cual acude con urólogo particular, quien solicita urotomografía que reporta hidroureteronefrosis bilateral, defecto de llenado vesical y engrosamiento de pared vesical (Fig. 1). Se realiza cistoscopia, con hallazgos de múltiples tumoraciones sésiles en trígono vesical que impiden visualización de los meatos ureterales, razón por la cual se realiza resección transuretral del tumor vesical (RTUV). Con reporte de histopatología de carcinoma poco diferenciado, compatible histológicamente con carcinoma urotelial variante en nidos, ulcerado, sin identificar tejido de muscular.

Por resultado de histopatología y persistencia de hematuria macroscópica a pesar de tratamiento médico y quirúrgico establecido previamente, la paciente decide acudir al servicio de urgencias del Hospital Regional ISSSTE de Puebla. Es valorada por el servicio de urología, se decide ingreso a piso y se programa para realización de Re-resección transuretral vesical (R-RTUV). Con hallazgos a la palpación bimanual: no se palpan tumores, vejiga no fija. En la cistoscopia se aprecian lesiones sésiles en fondo vesical, así como presencia de cicatrices posquirúrgicas en trígono vesical, sin evidencia meato ureteral derecho, meato ureteral izquierdo en hoyo de golf. Por hallazgos se realiza R-RTUV, con reporte de histopatología: cistitis crónica agudizada, ulcerada, fibras de músculo liso con inflamación crónica y cambios reactivos epiteliales, datos histológicos de malacoplaquia (Fig. 2). Inmunohistoquímica con células negativas para marcadores epiteliales (CKAE1/AE3), macrófagos positivos para CD68.

Por discrepancia con primer resultado histopatológico se realiza revisión de laminillas de primera y segunda resección transuretral vesical, que reporta: epitelio vesical ulcerado, con atipia epitelial en un contexto de inflamación crónica con predominio de macrófagos y células plasmáticas. Con reacciones inmunohistoquímicas negativas para marcadores epiteliales (CKAE1/AE3) y macrófagos positivos para CD68.

De acuerdo con el resultado de inmunohistoquímica se confirma diagnóstico de malacoplaquia, se inicia tratamiento antibiótico con levofloxacino 500 mg vía oral cada 24 horas por 14 días y antiinflamatorio con celecoxib 200 mg vía oral cada 12 horas por 14 días. En estudios posteriores a tratamiento se reporta examen general

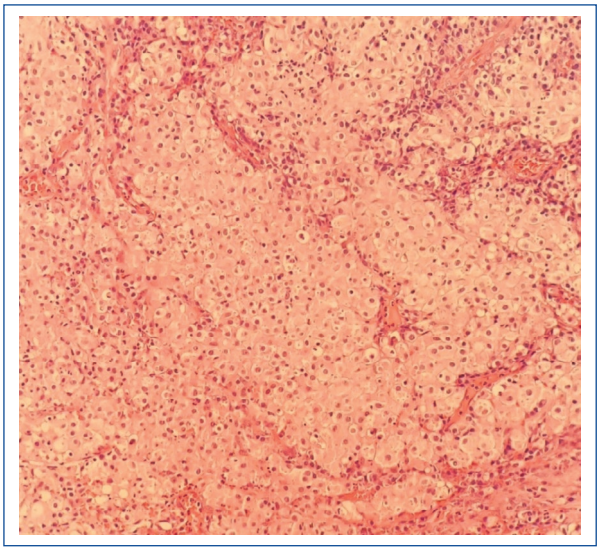

Figura 2. Tinción con hematosilina-eosina de tejido obtenido en R-RTUV, en la cual se aprecia tejido ureterial con infiltrado de macrofagos.

de orina sin evidencia de hematuria, urocultivo sin desarrollo bacteriano, citología con presencia de células inflamatorias crónicas. Se realiza cistoscopia tres meses posteriores al término de tratamiento, con hallazgos: epitelio sin evidencia de lesiones papilares o sésiles.

Discusión

La malacoplaquia, del griego *malakos* (blando) y *plakos* (placa), fue descrita por primera vez en 1902 por Michaelis y Gutmann y posteriormente caracterizada por von Hansemann en 1903. Es una enfermedad granulomatosa crónica, causada por un defecto en el sistema bacteriano fagocitario, asociado en el 40% de los pacientes a inmunocompromiso e infección por microorganismos (*E. coli* 89.4%)[2].

Es una patología extremamente rara, existen 49 reportes de 72 casos de 1986 a 2021. Presenta un pico hacia los 50 años de vida con una prevalencia cuatro veces mayor en mujeres sobre hombres. Puede afectar múltiples tejidos, siendo la vejiga el principal órgano comprometido en el 40% de los casos, otros tejidos afectados son los de riñón, próstata y uréter. En la vejiga se caracteriza por la presencia de nódulos, placas o úlceras asociada a síntomas del tracto urinario inferior y hematuria microscópica o macroscópica[2].

El diagnóstico de la malacoplaquia se basa en la combinación de hallazgos clínicos, estudios de imagen e histopatológico. En microscopio las lesiones se caracterizan por la presencia de histiocitos largos conocidos como células de von Hansemann, así como la presencia de esférulas basofilicas, extracitoplasmáticas o intracitoplasmáticas conocidas como cuerpos de Michaelis-Gutmann, los cuales se consideran patognomónicos de la enfermedad. Los estudios de imagen tienen utilidad para identificar hidroureteronefrosis, así como afección en estructuras extravesicales[3].

En cuanto al tratamiento, actualmente no hay pautas establecidas debido a la falta de estudios clínicos y la rareza de la enfermedad. El manejo se centra en el control de las infecciones del tracto urinario con antimicrobianos. Se han utilizado múltiples esquemas antibióticos, se ha demostrado tener una adecuada respuesta con sulfonamidas, rifampicina, doxiciclina, trimetoprima-sulfametoxazol y fluoroquinolonas. Así mismo, se ha visto que el uso de ácido ascórbico y betanecol aumentan los niveles intracelulares de monofosfato de guanina cíclica y con ello aumentan la función fagocítica de los macrófagos; y en conjunto con antimicrobiano han presentado buenos resultados[4,5].

El caso clínico presentado en el texto resalta la importancia de considerar la malacoplaquia como un diagnóstico diferencial en pacientes con síntomas del tracto urinario inferior y hallazgos anormales en los estudios de imagen. En este caso particular, la paciente fue inicialmente diagnosticada con carcinoma vesical debido a la similitud clínica y paraclínica entre ambas condiciones. Sin embargo, después de una revisión histopatológica más detallada se pudo establecer el diagnóstico de malacoplaquia.

En conclusión, la malacoplaquia es una enfermedad benigna poco común y desafiante de diagnosticar, que puede ser confundida con patología maligna. Se necesita una mayor conciencia y conocimiento sobre esta enfermedad para facilitar su detección y manejo adecuado. La investigación adicional sobre la patogénesis y los enfoques terapéuticos más efectivos ayudaría a mejorar el diagnóstico y tratamiento adecuado.

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Los autores declaran no tener conflicto de intereses.

Responsabilidades éticas

Protección de personas y animales. Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

Confidencialidad de los datos. Los autores declaran que han seguido los protocolos de su centro de trabajo sobre la publicación de datos de pacientes.

Derecho a la privacidad y consentimiento informado. Los autores han obtenido el consentimiento informado de los pacientes y/o sujetos referidos en el artículo. Este documento obra en poder del autor de correspondencia.

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