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LYMPHOEPITHELIOMA-LIKE CARCINOMA (LELC) OF THE URETHRA. A CASE REPORT

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RESUMEN

Introducción. El carcinoma similar al linfoepitelioma (LELC por sus siglas en inglés) es una variante de tumor muy infrecuente y agresiva, llamado así por su similitud histológica con linfoepiteliomas nasofaríngeos.
Presentación del caso. Hombre de 60 años que fue remitido al servicio de urología de un hospital público en la ciudad de Madrid (España) por una tumoración en el pene de 2 cm de diámetro de aproximadamente dos años de evolución. El análisis histopatológico reveló un tumor de crecimiento endofítico que ocupaba la porción ventral del glande, que infiltraba el meato uretral, cuerpo cavernoso, cuerpo esponjoso y uretra. Se decidió tratamiento quirúrgico (penectomía parcial) sin tratamiento neoadyuvante. El examen histológico confirmó el diagnóstico de carcinoma similar al linfoepitelioma de uretra.
Conclusión. El carcinoma similar al linfoepitelioma es un tumor poco frecuente en el aparato urinario y su aparición en el pene es excepcional. Cuando se localiza en esta zona el tratamiento generalmente combina cirugía y quimioterapia, y tiene buen pronóstico y mejores tasas de respuesta cuanto mayor es el componente linfoide en el tumor.

ABSTRACT

Introduction: Lymphoetepithelioma-like carcinoma (LELC) is a very rare and aggressive tumor variant, and it received that name because of its histological similarity to nasopharyngeal lymphoepitheliomas.
Clinical case: A 60-year-old man was referred to the urology service of a public hospital in the city of Madrid (Spain) due to a penile tumor of 2 cm in diameter that had been developing for approximately two years. The histopathological analysis revealed an endophytic growth tumor occupying the ventral portion of the glans, infiltrating the urethral meatus, corpus cavernosum, corpus spongiosum, and urethra. Surgical treatment was decided (partial penectomy) without neoadjuvant treatment. Histological examination confirmed the diagnosis of carcinoma similar to lymphoepithelioma of the urethra.
Conclusion: Lymphoepithelioma-like carcinoma is a rare tumor of the urinary tract and its occurrence in the penis is unusual. When located in this area, treatment generally combines surgery and chemotherapy, with a good prognosis and better response rates when there is a larger lymphoid component in the tumor.

INTRODUCTION

Urethral carcinomas are very rare and account for less than 1% of all malignant tumors of the urinary tract. Urothelial carcinoma is the most frequent histological type of primary urethral cancer (54-65%) and is usually located in the proximal urethra. Squamous cell carcinoma is the second most frequent type (16-22%), followed by adenocarcinoma (10-16%), and tends to be located in the distal urethra (1).

Lymphoepithelioma-like carcinoma (LELC) is a rare and aggressive variant of undifferentiated carcinoma. It receives its name due to its similarity to lymphoepithelioma, a nasopharyngeal carcinoma of higher prevalence among the Asian population, strongly related to Epstein-Barr Virus (EBV) infection, which is characterized by its high lymphocyte content (2,3). LELC in the genitourinary tract is very rare. It most frequently affects the bladder and rarely involves the distal urethra and penile region (4), so its diagnosis and treatment are not well established when it is located in these areas.

The clinical presentation, histologic and immunohistochemical features, and management of a case with LELC in the distal urethra are described below.

CASE PRESENTATION

A 60-year-old man, from Spain, was referred to the urology service of a tertiary care public hospital in the city of Madrid (Spain) in October 2019 due to a penile tumor that had been growing for 2 years. He had a medical history of pyrazolone allergy and severe obesity, with no family or surgical history of interest. The patient reported having a slow-growing stiffening in the distal penile area. He did not report urethral bleeding, pain during urination or discomfort during sexual intercourse. Physical examination revealed a 2 cm penile mass, ventral and distal, with involvement of the left corpus cavernosum in the distal area; no swollen lymph nodes were palpable.

In the first assessment made by the urology service, the following complementary tests were performed: 1) ultrasound (US) of the penis without intravenous injection of prostanglandin E (PGE), which showed a hypoechoic lesion in the distal corpus spongiosum of 10 mm and another in the left corpus cavernosum of 22.9 mm (Figure 1); 2) cystoscopy in which a mild stenosis of the fossa navicularis was identified (no alterations in the urethra and urinary bladder were found); 3) urine cytology test, which was negative for malignancy.

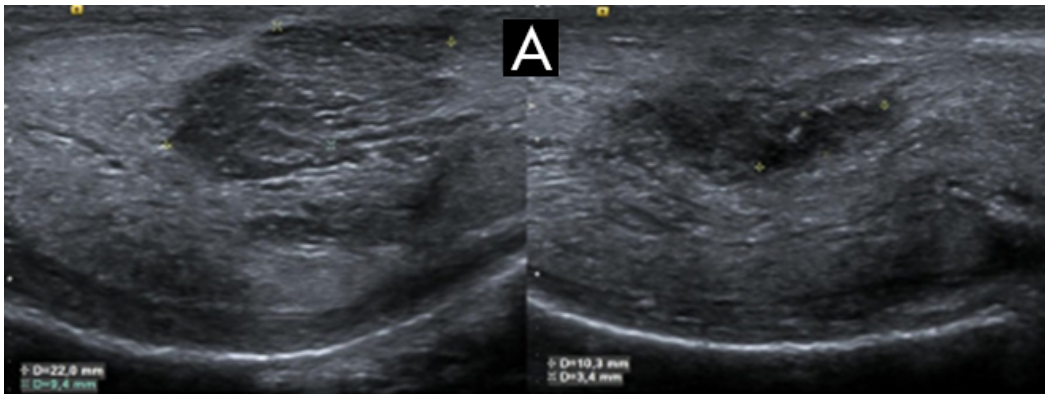

Figure 1. A) Ultrasound: lesion in the distal corpus spongiosum (right) and another in the left corpus cavernosum (left).
Source: Image obtained while conducting the study.

The patient was reevaluated at a second consultation with the urology service one month later and, after reviewing the results, a magnetic resonance imaging (MRI) scan was requested for tumor staging, but it could not be performed due to the patient's obesity. Since the MRI could not be performed, during a third consultation three weeks later, a positron emission tomography (PET/CT) with ^{18}F-fluorodeoxyglucose (FDG) was requested, showing pathological uptake in the distal portion of the penis coinciding with the tumor region, as well as suspicious nodes in the right inguinal ganglionic chain and in both external inguinal chains (Figure 2).

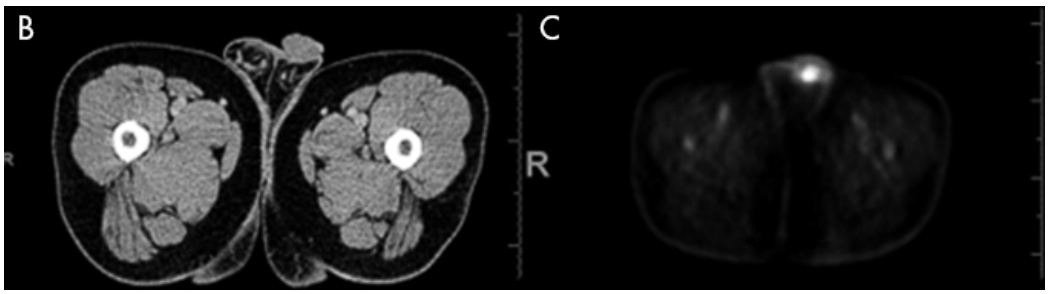

Figure 2. Preoperative scans of the penile lesion. B) Abdominal and pelvic CT and C) PET/CT with ^{18}F-FDG showing pathologic uptake in the penis.
Source: Image obtained while conducting the study.

The case was presented to the Oncologic Urology Committee in January 2020, three months after the first evaluation, and surgical treatment (partial penectomy) without neoadjuvant treatment was decided. The surgery took place four months after the first consultation. Penile skin degloving and placement of a tourniquet at the base of the penis were performed. The corpus cavernosum and corpus spongiosum affected by the lesion were dissected with a safety margin >5 mm.
The corpus cavernosum was stitched with simple 3-0 polypropylene (Prolene®)

sutures. Spatulation of the urethra and reconstruction of the urethral meatus were performed, and a Tiemann 18Fr bladder catheter was inserted. No lymphadenectomy was performed at the patient's request. There were no intraoperative or postoperative complications, and the patient was discharged from the hospital on the first postoperative day. Upon discharge, antibiotic prophylaxis was maintained with amoxicillin and clavulanic acid 1 g/oral every 8 hours for 14 days. The bladder catheter was kept in place for one month after surgery.

After surgery, a 3.6x3.5 cm surgical resection specimen including a foreskin fragment of 1.1 cm in length was sent to the Anatomic Pathology Service for histopathological analysis. After serial sections, a 3x2.4 cm endophytic growth tumor was identified occupying the ventral portion of the glans, which infiltrated the urethral meatus, corpus cavernosum, corpus spongiosum, and urethra. The deep resection margin and the balanopreputial groove were visually free of tumor infiltration (Figure 3).

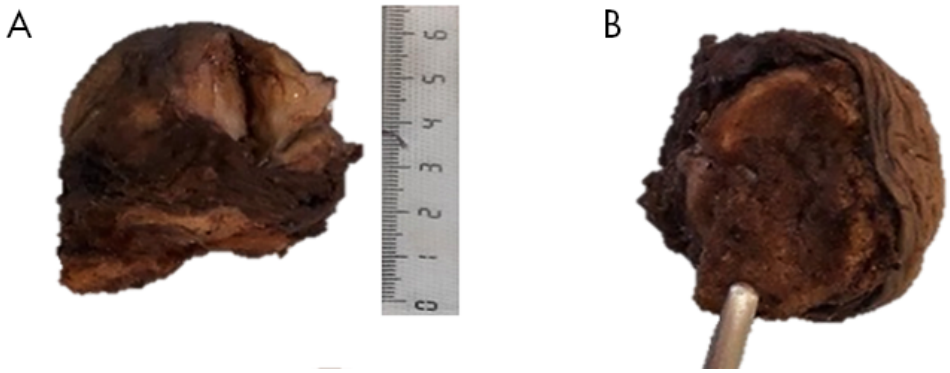

Figure 3. Surgical resection specimen taken during partial penectomy. Frontal (A) and posterior (B) views of the surgical resection specimen, showing an irregular whitish lesion that involved the urethra, corpus spongiosum, and corpus cavernosum bilaterally.

Source: Image obtained by the Anatomic Pathology Service while conducting the study.

The histological study showed that the urethral epithelium was infiltrated by a neoplastic proliferation growing in nests and trabecular pattern, consisting of atypical cells with large nuclei, evident nucleoli, and broad eosinophilic cytoplasm with indistinct margins, giving it the form of a syncytium. Tumor cellularity was accompanied by a lymphoid population composed of mature monomorphous lymphocytes (Figure 4-A). In the different sections examined, no images of lymphovascular or perineural invasion or neoplastic precursor lesions were identified. In the immunohistochemical analysis, tumor cellularity was positive for p16 and p63 markers and negative for Uroplakin-III, GATA3, and EBV. There was a lymphocytic inflammation consisting mainly of positive T-lymphocytes (CD3), with some groups of positive B-lymphocytes (CD20) (Figure 4 B-C-D). The final histopathologic diagnosis was "pure" LELC (stage T3, negative surgical margins).

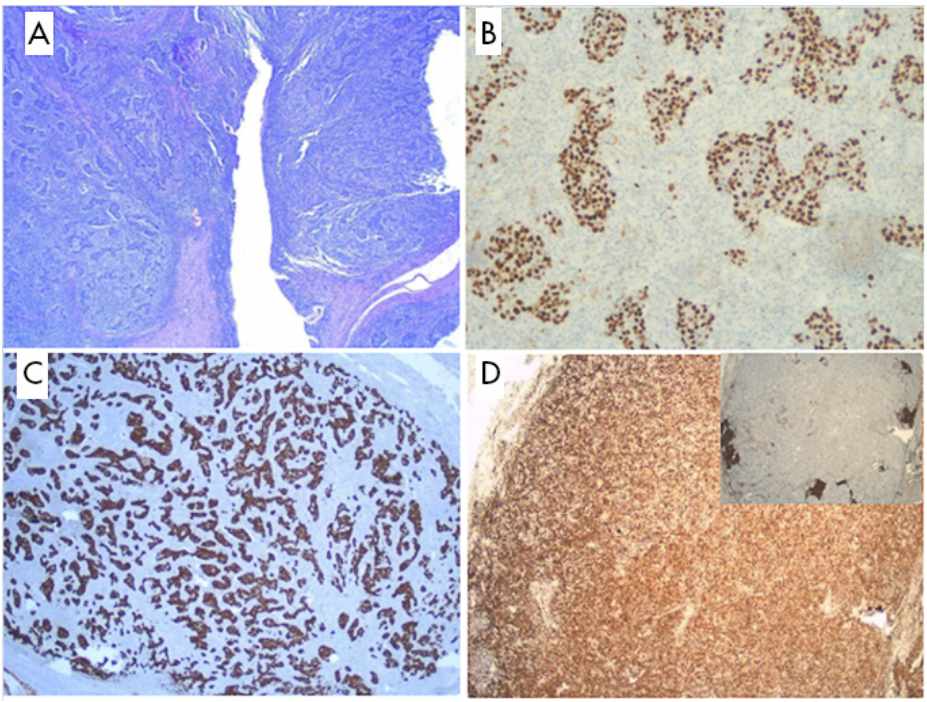

Figure 4. Panoramic view of the tumor made up of undifferentiated cells arranged in trabeculae and nests pattern, together with a lymphocytic inflammatory infiltrate (A); tumor cells showing intense and diffuse positivity for p40 and (B) p16; (C) inflammatory infiltrate consisting mainly of positive T-lymphocytes (CD3) (D) with isolated aggregates of positive B lymphocytes (CD20) (D) at the top right.
Source: Image obtained by the Anatomic Pathology Service while conducting the study.

The first follow-up appointment took place a month and a half after surgery, during which the bladder catheter was removed, and the patient was informed of the histopathological findings. During the performance of this procedure, good voiding dynamics were observed, as well as good aesthetic results, although the patient reported pain in the perineum when having erections. At the second follow-up appointment one month later, lymphadenectomy was proposed to the patient, but he refused any further treatment. Follow-up with the patient was lost before adjuvant treatment with chemotherapy (CT) could be proposed.

DISCUSSION

Lymphoepithelioma is a rare tumor commonly observed in nasopharyngeal tissue and is associated with EBV infection (3). The term lymphoepithelioma-like carcinoma is used to describe tumors with a characteristic appearance similar to lymphoepithelioma (large polygonal cells surrounded by lymphocytes) but located in other body sites. LELC has been described in various anatomical sites (mainly oropharynx, breast and cervix), but in these locations, unlike LELC originating in the nasopharynx, EBV has not been

detected within the tumor cells (5), but rather human papillomavirus (HPV) (5). However, no association between HPV and LELC in the urinary system has been described (6). In this case, in situ hybridization (ISH) for EBV was negative, and tumor cells showed strong positivity for the p16 marker, a surrogate marker for HPV, thus suggesting that HPV may also be associated with LELC originating in the urinary tract, as is the case in all other locations outside the nasopharynx.

The first case of LELC was described by Zukerberg *et al.* (7) in 1991 as a rare variant of urothelial carcinoma, characterized by a marked lymphocytic infiltration. Although LELC can occur in any part of the genitourinary tract, the most frequent location is the bladder with more than 140 cases described, followed by the upper urothelial tract with 28 cases (6). Urethral location is extremely rare with only one case described prior to this case report (8). In the urinary bladder and upper urothelial tract, LELC usually presents with gross hematuria (9-11). In the urethra, the only case described to date presented as a papillomatous overgrowth lesion with bleeding on friction in one patient (8).

Conventional imaging tests are unable to differentiate LELC from other more frequent tumors in these locations, while cystoscopy has shown that it is a solid, non-papillary tumor with a pathological anatomy and that ISH is the key to its diagnosis (9). In this case, physical examination was the basis for diagnosis and complementary tests such as US, cystoscopy and MRI were helpful for staging. PET/CT completed the regional and distant staging, and the histopathological study gave the definitive diagnosis.

Although LELC is a highly invasive tumor, lymph node metastases occur in only 10-20% of cases (12). It is an undifferentiated carcinoma and is made up of nests and trabeculae of undifferentiated cells with large pleomorphic nuclei, prominent nucleoli, indistinct cytoplasmic margins, and a syncytial appearance (12). The fundus contains a prominent lymphoid stroma including T and B lymphocytes, plasma cells, histiocytes, and occasional neutrophils or eosinophils. The ratio of the lymphoepithelial component has important prognostic and therapeutic implications and allows for the classification of LELC into 3 subgroups: a) pure (if all components are lymphoepithelial); b) predominant (more than 50% lymphoepithelial component); or c) focal (less than 50% lymphoepithelial component) (12). The best response rates are found in pure lymphoepitheliomas than in other variants. In these cases, CT is the mainstay of treatment, and conservative surgery may be indicated (12).

Since urethral LELC is so uncommon, there is little evidence in the literature on the most appropriate diagnosis and treatment, so currently only the treatment performed in this type of tumors located in the genitourinary tract, mainly in the bladder and upper urothelial tract, can be extrapolated. Although surgery is the preferred treatment in most cases, including this one, it is not well established due to the low frequency of this type of tumor. The cases described in

the literature on LELC in the bladder and kidney suggest that the lymphoid and inflammatory component favors a strong immune response against the tumor cells, thus maximizing the effect of CT when the lymphoepithelial component is greater. Therefore, better response rates are obtained in pure lymphoepitheliomas than in the other variants, and in these cases, CT is the mainstay of treatment and more conservative surgery may be indicated (12).

Several CT schemes have been used, including adjuvant methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) or gemcitabine and cisplatin (10). In this case, follow-up was lost before adjuvant treatment with CT could be proposed.

As reported by Jabbour *et al.* (10), a study conducted by Yoshino *et al.* in 13 patients demonstrated that the combination of transurethral resection (TUR) of the bladder plus CT is an effective treatment in patients with pure or predominant LELC, with no recurrence within 72 months after treatment. On the other hand, they concluded that the response to chemotherapy in focal lymphoepitheliomas is weaker, requiring more aggressive surgeries and multifocal therapies (10).

Radiotherapy offers another option with good results, especially in pure and predominant LELC in patients with comorbidities who are not suitable for surgery or would not tolerate chemotherapy. The prognosis of pure and predominant LELC is positive with a disease-specific survival rate of 93%, whereas it is almost 0% in focal LELC (12).

CONCLUSION

LELC in the urinary tract is a rare malignant tumor, and this is the second case of urethral location described in the literature. Therefore, the diagnosis and treatment of this type of tumor in the genitourinary tract is different from that of tumors located in the nasopharyngeal tissue. Histological and immunohistochemical study is a cornerstone for its diagnosis since it may be similar to other tumors both macroscopically and clinically. HPV may play a role in its etiology, although it is necessary to identify more cases to define this association. More research is needed to find the most appropriate treatment; however, chemotherapy seems to yield very good response rates when the tumor is pure or predominant.

PATIENT'S PERSPECTIVE

The patient was initially satisfied with the results of his treatment. Although he claimed to experience difficulties during sexual intercourse and to feel bad about his body image after penile surgery, his satisfaction improved in the following visits. Since he was lost to follow-up early, so his long-term perspective is not known.

CONFLICTS OF INTEREST

None stated by the authors.

ETHICAL CONSIDERATIONS

The patient signed an informed consent to treat and disclose his medical records for scientific and academic purposes.

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