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Brief report – Bladder cancer

Inverted urothelial papilloma: Our clinical experience

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A B S T R A C T

A study of inverted urothelial papilloma in our area.
Material and methods: A study was conducted of inverted urothelial papillomas diagnosed at our center from January 1994 to December 2007. This was a retrospective and prospective study with a descriptive statistical analysis: urological history, reason for consultation, diagnostic methods, tumor focality, follow-up method, prognosis, and recurrence. SPSS software version 13 was used for statistical analysis.
Results: Fourteen inverted papillomas were diagnosed in the study period in patients with a median age of 59 years. The presenting complaint was hematuria in 7 patients (50%), followed by low back pain in 2 patients (14.28%), and irritative syndrome in 1 patient (7.14%). The tumor was incidentally diagnosed in 4 patients (28.5%). A single relapse/recurrence occurred in a low-grade tumor during the follow-up period.
Conclusions: Prognosis, recurrence, and malignant potential of this tumor are unclear, and controversy exists in the literature on this subject. Thus, although we think this is a benign tumor, we advise follow-up as if it were a low-grade urothelial tumor.

Papiloma invertido urotelial: nuestra experiencia clínica

Palabras clave:
Papiloma invertido
Neoplasia urotelial
Estado actual

R E S U M E N

Estudio de los papilomas invertidos uroteliales en nuestra área.
Material y métodos: Realizamos un estudio de los papilomas invertidos uroteliales diagnosticados en nuestro centro entre enero de 1994 y diciembre de 2007. Se realizó un estudio retrospectivo y prospectivo con análisis estadístico descriptivo: antecedentes urológicos, motivo de consulta, método diagnóstico, focalidad tumoral, método de seguimiento, pronóstico y recurrencia. Se realizó un estudio estadístico con el software SPSS versión 13.

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Resultados: En el período de estudio se han diagnosticado 14 papilomas invertidos, con una mediana de 59 años. El motivo de consulta fue hematuria en 7 enfermos (50%), seguido de dolor lumbar en 2 enfermos (14,28%) y de síndrome irritativo en 1 enfermo (7,14%), fue diagnosticado en 4 enfermos (28,5%) de manera incidental. Durante el período de seguimiento sólo se produjo una recidiva/recurrencia en un tumor de bajo grado.

Conclusiones: El pronóstico, la recurrencia y el potencial de malignización de este tumor no están claros, existiendo controversias en la literatura médica mundial, hecho por el cual, aunque desde nuestro punto de vista su naturaleza es benigna, aconsejamos un seguimiento como si se tratase de un tumor urotelial de bajo grado.

Introduction

Inverted urothelial papilloma was first described by Pasckins in 1927, and defined by Potts and Hirst in 1963[1]. Histologically, it is a benign tumor characterized by endophytic epithelial growth. Inverted urothelial papilloma accounts for 2.2% of all urothelial cancers[2-5]. The ureteral location is uncommon, and no more than 15 cases have been found in the international medical literature[6]. The purpose of this study was to review our series and assess the progress of these patients, determine our region's incidence of recurrence and malignization, and compare it to other reviews.

Material and methods

We conducted a retrospective and prospective study of inverted urothelial papillomas diagnosed in our hospital from January 1994 to December 2007. The descriptive statistical study was done with the SPSS system version 13. The variables analyzed were gender, age, habits, personal history, urological history, reason for consultation, diagnostic method, tumor focality, follow-up method, prognosis, and recurrence.

Results

Between January 1994 and December 2007, 14 patients were diagnosed with inverted urothelial papilloma at our hospital. Thirteen patients were males and one was a female. Patients' mean age at the time of diagnosis was 57.7 years, the median age was 59, and the range 23 to 82 years.

Nine patients (64.2%) were smokers or had quit smoking within the two previous years. The urological history of interest included three patients (21.42%) with severe prostatism (IPSS score above 15), two patients (14.28%) had had a history of nephritic colics, and one patient had undergone resection of a low grade bladder tumor (UICC pTa GI).

The presenting complaint was hematuria in seven patients (50%), followed by low back pain in two (14.28%) and irritative syndrome in one (7.14%). The tumor was diagnosed incidentally in four patients (28.5%).

The initial diagnostic method was ultrasound for seven patients (50%), cystoscopy for five (35.71%), and intravenous urography for two (14.28%). The tumor was in the bladder in 13 patients, and in the left sacral ureter in one case; one patient had a bladder tumor and an associated papilloma in the prostatic urethra. Of the tumors in the bladder, 8 were in the trigone, four on the lateral walls, and one in the fundus; one patients had a double lesion in the trigone and the prostatic urethra. Seven patients (92.8%) had a single tumor, and one (7.2%) had multiple tumors (two locations).

Pathologically, the lesion in 100% of patients was pure inverted papilloma with no areas of atypia or urothelial carcinoma. Only in six cases was the papilloma classified in subtypes: 4 were glandular, and 2 trabecular (fig. 1).

Treatment consisted of transurethral resection in 100% of the bladder cases, and segmental ureterectomy for the patient with inverted papilloma in the ureter (fig. 2).

For six patients (42.8%), the chosen follow-up method was ultrasound; cystoscopy was the follow-up method for six patients (42.8%). One patient (7.14%) was followed-up with intravenous urography, and one was not followed-up.

The mean follow-up was 63.71 months, with a median of 36 months and a range of 4 – 94 months. One relapse, in the form a low-grade urothelial tumor, occurred during follow-up, which represents 7.14%; the relapse occurred in the patient with prior resection of a low-grade tumor. No

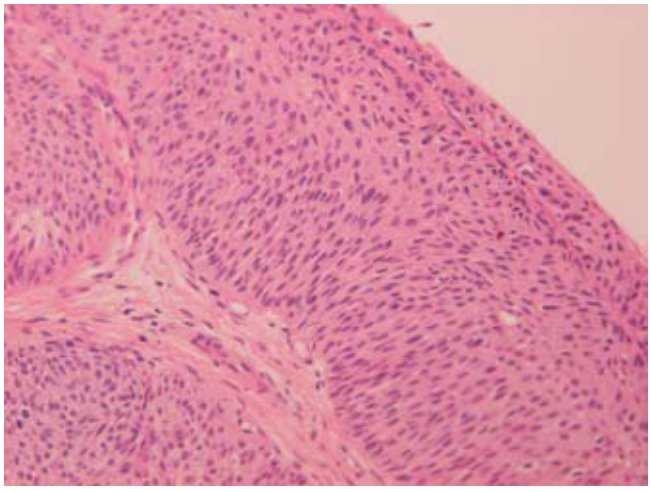

Figure 1 – Low magnification microscopy.

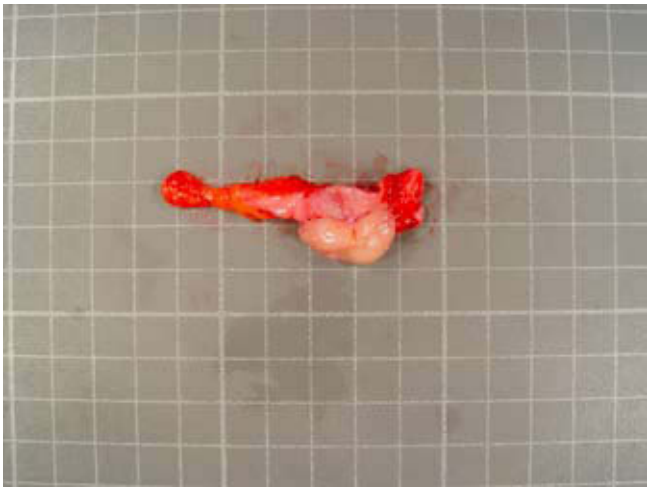

Figure 2 – Surgical piece from the segmental ureterectomy for inverted papilloma.

metastases or disease-specific mortality occurred during the period covered by this study.

Discussion

The age at which this tumor appears is between the third and seventh decade of life; the sixth and seventh decades are the periods with highest incidence[1,3,7]. Some childhood cases have been described[10]. The condition is more common in males, with a ratio of 5:1[1,3] (but there are series with lower ratios of 1.6:1)[9], a more pronounced difference than for bladder cancer, which has a male/female ratio of 2:1. Inverted papilloma accounts for 1–2.2% of urothelial bladder malignancies[2,3,9]. The most common location is the bladder (90%)[2,6,7,9]. In the bladder, the most usual location is the trigone[9], followed by the fundus and the neck[1,7]. Location in the urethra is uncommon (3.6% of inverted papillomas), and if located here, most are in the prostatic urethra; only two cases have been described in the anterior urethra. Upper urinary tract location is uncommon (5–20%)[6]. Inverted urothelial papilloma in the ureter is rare, with no more than 80 cases described in the international medical literature, representing 12% of inverted urothelial papillomas. The mid- or distal ureter are the most common locations[5,6]; in the upper urinary tract, the renal pelvis is the most rare site, accounting for about 7% of inverted papillomas[4]. Synchronous or metachronous multifocality is described in 10% of patients[7].

Etiology is idiopathic; several authors define this condition as a low-grade urothelial cancer, while others assert that it is a hyperplastic reaction secondary to a chronic inflammatory process[9]. There are several theories about the pathogenesis: chronic inflammation, hyperplasia of the glands of Home, Von Brunn and/or Albarran, and urinary obstruction[1,2,5]. The inflammatory-obstructive theory is supported by the frequent location of the tumor in the trigone and its common association with prostate hyperplasia[2,4]; however, other authors have found this association in only 27% of cases, or irritative or obstructive factors.

The most common symptoms are hematuria and low urinary obstructive symptoms[1,7,9]. Del Castillo et al[9] report a predominance of urinary urgency as the main complaint in up to 44% of cases, since most lesions are located in the trigone. The symptoms of inverted papillomas in the upper urinary tract are hematuria and kidney pain secondary to urinary obstruction[6].

Radiologic findings are unspecific; space-occupying defects are found in 30–50% of cases, and the images are indistinguishable from bladder cancer. Ultrasound is often the first diagnostic method, showing in most cases space-occupying lesions[9], and sometimes pedunculated lesions (a feature that suggests this diagnosis[7]). Most urologists continue to use cystoscopy for confirmation[9]; these tumors are seen as small nodular, raised, solid tumors, and are sometimes pedunculated; a papillary aspect is not characteristic because growth is endophytic and the epithelium covering it is normal[9]. Urinary cytology has no diagnostic value because inverted papillomas are covered with normal urothelium and grow inside the wall; the few published cases with positive cytology are papillomas associated with urothelial tumor.

The most exhaustive pathological definition of inverted papilloma is provided by Henderson et al[5]: a lesion of inverted configuration, a covering layer of normal epithelium, uniformity of the lining of epithelial cells, few or absent mitoses, microcysts (crypts), and squamous metaplasia. Kunze described two types; while they have no prognostic implications, they do have a pathogenesis implication: trabecular and glandular. The trabecular type arises from a proliferation of basal cells of the transitional epithelium; the glandular type's growth is a process in three stages: formation of Von Brunn nests, progression to cystitis cystica and glandularis, and subsequent transformation into inverted papilloma. Other authors distinguish two types of inverted papilloma: Type I, with benign characteristics, and Type II, with malignancy potential. There are currently no criteria to distinguish between the two[5]. Macroscopically, the lesions are characteristically single tumors with a papillary appearance, a wide implantation base, and a smooth surface. Microscopically, it is an epithelial lesion consisting of normal urothelial cells with palisading and no atypia, forming a trabecular subepithelial growth pattern with occasional cystic areas that contain eosinophilic PAS+ material[1,7]. Based on the absence of mitoses and the low incidence of recurrence and malignization, the tumors are considered benign[3]. Despite the benign nature, there are cases of coexistence with urothelial carcinoma and of carcinomatous degeneration[6]. These tumors are considered benign because of their histological features and their natural history. However, upon finding high mitotic indices, some authors tend to classify them as tumors with low aggressiveness, although an elevation of the mitotic index has no proven role as a precursor of malignancy, and must be considered only a risk marker[7].

Despite Henderson's criteria, differential diagnosis is difficult, especially with conditions such as cystitis cystica, cystitis glandularis, and low-grade urothelial carcinoma.

Treatment for an inverted bladder papilloma is transurethral resection; intravesical chemotherapy or immunotherapy are not indicated unless there is an associated urothelial tumor.

Inverted papilloma of the upper urinary tract has been traditionally treated with nephroureterectomy[6,8,9] with bladder cuffing, but the current tendency towards minimally invasive procedures supports ureteral resection[1] or conservative surgery[1,6-8].

The potential for malignancy and the prognostic value of the urothelial inverted papilloma remain controversial. In the 1970s, it was considered a benign tumor; recurrences and malignization reported by several authors suggested a low potential for malignancy[2]; other data, such as the low rate of recurrence compared to urothelial tumors (5 vs. 60%), the fact that lesions are single (95%) and lack a capacity for metastization, support a benign character[2,5].

The potential for malignization is not well defined; some authors consider this a benign tumor[3]; the association with urothelial carcinoma is common; there have been cases of malignization and recurrence described[2,6]. Association with a concomitant or previous urothelial carcinoma varies from 20[3] to 54.8%[2], depending on the series. Nuñez et al found an association with urothelial neoplasm in 45.8% of cases, and observed that the urothelial tumor and the inverted papilloma are part of the same urothelial neoplasm[2]; this would explain multiplicity, recurrences, degeneration, and even the coexistence within the papilloma of areas of urothelial carcinoma with inverted growth[3,5]. Some series have found that the behavior of inverted urothelial papilloma is that of a low-aggressiveness transitional neoplasm[2].

Given the uncertainty regarding prognosis and potential for recurrence and/or malignization, several authors quantified differences in ploidy and proliferative cell activity with MIB-1 and *p53* in patients with associated urothelial carcinoma and in those without urothelial carcinoma; they found no significant differences and concluded that these markers have no prognostic value in inverted papilloma. Valero et al found that cases with an overexpression of nuclear antigen Ki-67 have a poorer prognosis[10]. Brousard et al analyzed the significance of cell atypia in inverted papillomas and the potential degeneration to low-grade carcinoma or recurrence, and found no differences in the recurrence rates of inverted papillomas with and without atypia.

Based on the discrepancies between the malignization potential and recurrence, most authors recommend follow-up. Due to the high rate of recurrence (close to 15%) and the high association with urothelial tumor, Núñez et al recommend a follow-up similar to that offered in cases of low-grade bladder tumors[2].

Conclusions

Inverted urothelial papilloma is an uncommon lower urinary tract tumor representing about 2% of urothelial tumors. Definitive diagnosis is provided by the anatomopathological examination, for which strict histological criteria are required. There is currently no conclusive evidence of the biologic behavior of the inverted papilloma; research is being done regarding the value of the overexpression of nuclear antigen Ki-67 and protein p53. Prognosis, recurrence, and malignant potential of this tumor are unclear, and controversy exists in the international medical literature on this subject. Although we think that this is a benign tumor, we advise follow-up as if it were a low-grade urothelial tumor.

Conflict of interest

The authors state that they have no conflicts of interest.

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