Clinical versatility of the inflammatory pseudotumor in urology

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KEYWORDS
Inflammatory pseudotumor; Myofibroblastic proliferation; Bladder; Renal pelvis; Epididymis

Abstract
Objective: The inflammatory pseudotumor is a rare lesion, having benign behavior and some histological heterogeneity that appears in the genitourinary tract. A series of urogenital inflammatory pseudotumors are reviewed with emphasis on their clinicopathological and immunohistochemical characteristics.

Materials and methods: A retrospective study on the causistics treated between January 1981 and December 2010 was performed. It identified the cases of inflammatory pseudotumor with urogenital localization. The variables age, gender, symptoms, topography, treatment and anatomopathological and immunohistochemical characteristics of each case were analyzed.

Results: A total of 8 cases of the urogenital-located inflammatory pseudotumor are described. Of these, 6 were located in the bladder, one in the kidney and one in the epididymis. Mean age of the patients was 46.75 (±19.84) years. Tumor presentation symptoms were macroscopic hematuria, single symptom or accompanied by symptoms of the lower urinary tract and inguinoscrotal mass. With regard to treatment in the cases of bladder localization, transurethral ± cystectomy were performed. In the case of kidney localization, treatment was made by means of pyelotomy and exeresis, and in the case of epididymis localization, simple exeresis was performed. The anatomopathological study showed inflammatory pseudotumor in every case, having a mesenchymal and myxoid appearance, with fusiform cells of eosinophil cytoplasm, with presence of frequent inflammatory cells. The most common immunohistochemical pattern shows positivity for the muscle-specific actin (HHF-35), vimentin and negativity for protein S-100. ALK-1 was positive in 87.5% of the cases.

Conclusion: The inflammatory pseudotumor is a condition having good prognosis which, when there is a good histopathological and immunohistochemical diagnosis, every urologist should recognize and distinguish in order to carry out as conservative a surgical treatment as possible.

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PALABRAS CLAVE
Pseudotumor inflamatorio; Proliferación pseudosarcomatosa miofibroblástica; Vejiga; Pelvis renal; Epididimo

Versatilidad clínica del pseudotumor inflamatorio en Urología

Resumen
Objetivo: El pseudotumor inflamatorio es una lesión rara, de comportamiento benigno y cierta heterogeneidad histológica que aparece en el tracto genitourinario. Se revisan una serie de pseudotumores inflamatorios urogenitales poniendo especial énfasis en sus características clínico-patlológicas e inmunohistoquímicas.

Material y métodos: Análisis retrospectivo de la casuística tratada entre enero de 1981 y diciembre de 2010 que identifica los casos de pseudotumor inflamatorio de localización urogenital. Se analizan las variables edad, sexo, clínica, topografía y tratamiento, y las características anatomopatológicas e inmunohistoquímicas de cada caso.

Resultados: Se describen un total de 8 casos de pseudotumor inflamatorio de localización urogenital, de los cuales 6 se localizaron en la vejiga, uno en el riñón y uno en el epididimo. La edad media de los pacientes fue 46,75 (±19,84) años. Los síntomas de presentación tumoral fueron hematuria macroscópica, monosintomática o acompañada de sintomatología del tracto urinario inferior y masa ininguino-escrotal. En cuanto al tratamiento en los casos de localización vesical se realizó resección transuretral ± cistectomía; el caso de localización renal se trató mediante pielotomía y exéresis y el de localización epididimaria mediante exéresis simple. El estudio anatomopatológico evidenció pseudotumor inflamatorio en todos los casos, de aspecto mesenquimal y mixoide con células fusiformes de citoplasma eosinófilo, con presencia de frecuentescélulas inflamatorias. El patrón inmunohistoquímico más común mostró positividad para actina muscular-específica (HHF-35), vimentina y negatividad para proteína S-100. ALK-1 resultó positivo en el 87,5% de los casos.

Conclusión: El pseudotumor inflamatorio es una entidad de buen pronóstico que, con un buen diagnóstico histopatológico e inmunohistoquímico, todo urólogo debe conocer y distinguir para realizar un tratamiento quirúrgico tan conservador como sea posible.

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Introduction

The inflammatory pseudotumor is a rare lesion, histologically composed of myofibroblastic spindle cells that are accompanied by an inflammatory infiltrate and which has its origin in the soft tissues and viscera. Because of its histologic heterogeneity, it has received many names over the past years: inflammatory pseudotumor, fibromyxoid pseudosarcoma, nodular fasciitis, pseudosarcomatous myofibroblastic proliferation, and postoperative spindle cell nodule. In addition to the important fibrosis and vascularization, limited in most cases to the lamina propria of the tissue, the pseudotumor affects on many occasions the muscularis mucosae of the tissues where it is located.1,2

The inflammatory pseudotumor of the bladder was first described by Roth in 19801,3,4 in a 32-year-old woman who had recurrent urinary tract infections, accompanied by episodes of hematuria associated with bladder injury. Subsequently, Nochomovitz and Oreinstein implemented in 1985 the appropriate terminology to describe bladder injury.5 Mostofi and Price6 characterized the lesions of the spermatic cord, describing the histopathologic similarity with the fibroxanthoma.7 The renal inflammatory pseudotumor, an extremely rare entity within the inflammatory pseudotumors, has been described both in the pelvis and ureter and in the renal parenchyma.8

Among the first cases, the authors advocated a higher incidence of cases among females, although in recent cases reviewed, male predominance is objectified (3:1).9,10 Although most cases of inflammatory pseudotumor occur in young adults, some cases have been reported in an age range of 3–89 years.1,10

The topographic versatility of the pseudotumor evidences that the injury occurs more frequently in lung tissue, with cases reported in various organs such as the stomach, pancreas, spleen, or central nervous system. With regard to the urinary tract, the most common location is the fundus of the bladder, followed by the lateral sides and back.1 Its presentation in the bladder trigone is exceptional, and it raises the possibility that its origin is retrotrigonal by primary invasion. There have been cases of inflammatory pseudotumor in the female urethra and prostate, and even intra-and paratesticular.

Obviously, the location of the inflammatory pseudotumor conditions the presentation and the clinic, although the most frequent is the asymptomatic presentation. One third of the patients with this condition have a syndrome characterized by fever, growth retardation, weight loss, discomfort, anemia, thrombocytopenia, polyclonal hypergulbinemia, and increased sedimentation rate. This symptomatic courtship disappears once the excision of the mass is carried out, relating the reappearance of the medical profile to the recurrence of the disease.

In this paper, we reviewed the casuistry of urogenital inflammatory pseudotumor diagnosed and treated over three decades in different hospitals, the characteristics of this entity and its versatility of urologic appearance, and the various treatment options.

Materials and methods

We performed a retrospective study that includes the casuistry of three Spanish hospitals from January 1981 to
December 2010, identifying the cases of inflammatory pseudotumor of the urogenital tract. We analyzed the variables age, sex, clinical presentation, topography of the lesion, surgical treatment performed, and immunohistochemical and pathological characteristics. A descriptive statistical analysis was performed, using mean and standard deviation in the quantitative variables, while we used percentages in the qualitative variables.

Results

A total of 8 cases of inflammatory pseudotumor of urogenital location are described, of which 6 (75%) were located in the bladder (4 on the back and bottom, one at the dome, and one on the anterior bladder side) (Fig. 1), one (12.5%) in the kidney (middle calyceal group), and one (12.5%) in the epididymis. The mean age of the patients was 46.75 years (±19.84). The male:female ratio was 6:2. The mean tumor size, measured as maximum diameter at the macroscopic piece was 5.37 cm (±3.55). The presenting symptoms of tumor were monosymptomatic gross hematuria in 3 out of 8 cases (37.5%), hematuria accompanied by bladder symptoms in 2 out of 8 (25%), lower urinary tract symptoms in 2 out of 8 (25%), and inguinocrotal mass in 1 out of 8 cases (12.5%).

As to the treatment performed, in the cases of bladder location, transurethral resection of bladder tumors (TUR-B) was carried out only in 2 out of 6 cases (33.3%) (Fig. 1), partial cystectomy in 3 out of 6 (50%), and total cystectomy in 1 out of 6 (16.6%) (Fig. 2). The case of kidney localization was treated by extended pyelotomy with excision of the tumor lesion, and the one of epididymal localization by excision of the mass along with inguinal herniorrhaphy. Both in the case of the renal pseudotumor and in the testicular one, conservative treatment was based on the benign nodular aspect of the lesion.

The pathological study predominantly showed a histological pattern with compact proliferation of myofibroblastic spindle cells and myxoid regions, diffuse swelling, and small aggregates of plasma cells. Sometimes ganglion-like myofi-broblasts with little or no presence of mitosis (Fig. 3) were shown. In other cases, there was atypical pattern with

Figure 1  Bladder inflammatory pseudotumor treated with exclusively repeated TUR-B. (A) Preoperative CT; (B) postoperative control.

Figure 2  Macroscopic image of bladder inflammatory pseudotumor (12 cm × 9.5 cm) treated with total cystectomy and orthotopic bladder substitution.

Figure 3  Typical inflammatory pseudotumor, spindle cell proliferation in a myxoid stroma and vascularized. The myofibroblastic spindle cells with vesicular nucleus and prominent eosinophilic nucleolus are accompanied by inflammatory cells (H–E, 40×).
Table 1  Clinicopathologic and immunohistochemical characteristics of patients with inflammatory pseudotumor.

<table>
<thead>
<tr>
<th>No. case</th>
<th>Age-sex</th>
<th>Location</th>
<th>Size</th>
<th>Clinical presentation</th>
<th>Imaging methods</th>
<th>Treatment</th>
<th>Histology of the lesion</th>
<th>Immunohistochemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16-Man</td>
<td>Bladder (back and bottom)</td>
<td>3.5 cm</td>
<td>Monosymptomatic gross hematuria</td>
<td>IVU</td>
<td>Partial cystectomy</td>
<td>Mesenchymal (spindle cells with eosinophilic cytoplasm and inflammatory cells)</td>
<td>HHF-35 (+), vimentin (+), desmin (−), S-100 (−), ALK-1 (+)</td>
</tr>
<tr>
<td>2</td>
<td>49-Woman</td>
<td>Bladder (back)</td>
<td>4.5 cm</td>
<td>Dysuria, suprapubic pain</td>
<td>IVU</td>
<td>Partial cystectomy</td>
<td>Mesenchymal-myxoid with few mitoses</td>
<td>Unavailable</td>
</tr>
<tr>
<td>3</td>
<td>29-Man</td>
<td>Bladder (dome and anterolateral side)</td>
<td>9 cm</td>
<td>Hematuria, voiding syndrome</td>
<td>CT</td>
<td>Repeated TUR-B</td>
<td>Mesenchymal-myxoid</td>
<td>HHF-35 (+), AE1-AE3 (+), vimentin (+), desmin (+), S-100 (−), ALK-1 (+)</td>
</tr>
<tr>
<td>4</td>
<td>74-Man</td>
<td>Bladder (anterior side)</td>
<td>12 cm × 9.5 cm</td>
<td>Dysuria, pollakiuria, lower urinary tract symptoms</td>
<td>CT NMR</td>
<td>Repeated TUR-B + total cistectomy + orthotopic urinary diversion</td>
<td>Myxoid with little atypia without evidence of mitosis</td>
<td>HHF-35 (+), AE1-AE3 (+), vimentin (+), desmin (mild +), S-100 (−), MyoD1 (−), ALK-1 (+)</td>
</tr>
<tr>
<td>5</td>
<td>70-Man</td>
<td>Epididymis</td>
<td>1 cm</td>
<td>Inguinoscrotal mass</td>
<td>US</td>
<td>Inguinal herniorrhaphy + left epididymis mass excision</td>
<td>Myxoid with mild mitosis</td>
<td>HHF-35 (+), vimentin (+), desmin (−), S-100 (−), ALK-1 (+)</td>
</tr>
<tr>
<td>6</td>
<td>35-Woman</td>
<td>Kidney (middle caliceal group)</td>
<td>2 cm × 3 cm</td>
<td>Monosymptomatic gross hematuria</td>
<td>US IVU CT NMR</td>
<td>Enlarged pyelotomy with lesion excision</td>
<td>Mesenchymal-myxoid</td>
<td>HHF-35 (+), desmin (−), CD34 (−), keratin (−), ALK-1 (−)</td>
</tr>
<tr>
<td>7</td>
<td>46-Man</td>
<td>Bladder (back)</td>
<td>4 cm</td>
<td>Monosymptomatic gross hematuria</td>
<td>US CT</td>
<td>TUR-B</td>
<td>Mesenchymal-myxoid with invasion of muscularis propria</td>
<td>HHF-35 (+), vimentin (+), desmin (−), S-100 (−), ALK-1 (+)</td>
</tr>
<tr>
<td>8</td>
<td>55-Man</td>
<td>Bladder (right, lateral side and back side)</td>
<td>6 cm</td>
<td>Gross hematuria, voiding syndrome</td>
<td>CT IVU US</td>
<td>TUR-B + partial cystectomy</td>
<td>Mesenchymal-mixoide</td>
<td>HHF-35 + vimentin + desmin – S-100 – ALK-1 +</td>
</tr>
</tbody>
</table>

US: ultrasound; NMR: nuclear magnetic resonance; CT: computed tomography; IVU: intravenous urography.
myxoid stroma and spindle-cell eosinophilic proliferation, and important vascularization that can be confused with a granulation tissue or inflammatory processes, and more rarely also with malignant mesenchymal processes (Fig. 4). A final pattern showed exclusively mesenchymal predominance with presence of abundant inflammatory cells (Table 1).

The most common immunohistochemical pattern showed positivity for muscle-specific actin (HHF-35) and vimentin, together with negativity for the S-100 protein. In two of the cases, marked immunoreactivity was observed for vimentin and cytokeratins (AE1–AE3). We carried out additional staining that showed multifocal moderate immunoreactivity of intracytoplasmic granular type for ALK-1, which was positive in 87.5% of the cases. Negativity was also shown for MyoD1, cytokeratins 7 and 20, and EMA (Table 1).

Discussion

It is necessary to know the clinical versatility of the inflammatory pseudotumor to distinguish it with greater probability from other similar entities, but with different management and prognosis.1 The teaching learned leads us to propose in these cases a treatment as conservative as possible and avoid radical treatments in most cases. The inflammatory pseudotumor can be confused with malignancies such as bladder leiomyosarcoma, rhabdomyosarcoma (more common in childhood), bladder carcinosarcoma, or ulcerative interstitial cystitis.2,4,10–13 The use of immunohistochemical markers and even electron microscopy is essential in achieving a correct differential diagnosis with these entities.

Vimentin reactivity and muscle-specific actin are observed in more than 90% of the cases (93–100%).1 Desmin, which is positive in 5–80% of the cases reviewed, is quite unspecific since it can be expressed in both sarcomas and inflammatory pseudotumors.4,10,11,14 Other markers, such as myogenin (MYCF-4, Myo-D), factor VIII, and cytokeratin also show occasional positivity. TP53 positivity is rare and it is associated with recurrences and malignant transformations. Recently, it has been defined that the anaplastic lymphoma kinase (ALK) marker is of great importance in establishing a correct diagnosis.14–16 Several cytogenetic abnormalities have also detected alterations in the karyotype of the inflammatory pseudotumor. 50–60% of the cases reviewed have aberrations on the short arm of chromosome 2, regions p21–p23, involving the mentioned ALK. These changes are rarer in adult patients older than 40 years. In fact, the detection of ALK at the C-terminal end is shown as the most efficient method to detect oncoproteins in inflammatory pseudotumors.16 This specificity is due to the low expression of ALK proteins in non-tumor myofibroblasts, which warns of the presence of a mechanism of oncogene activation in these cells. This way, this tumor can be better distinguished from a leiomyosarcoma or sarcomatoid carcinoma.14,15 By means of in situ hybridization techniques (FISH), we have also achieved to show these alterations.10 In any case, it is noteworthy that the inflammatory component is not related to ALK activation.

On the other hand, some authors advocate the presence of alterations in chromosome 12 (q13 and q15 regions), whose target are the HMGIC gene (also known as HMGA2), and the presence of viral DNA in the karyotype of the pseudotumor or cytoplasmic inclusions similar to those evidenced in Chlamydia infections.4

Tumor treatment must be directed, in any case, to surgical exeresis thereof. The cases reviewed in the literature include both radical excisional treatment and conservative surgery.1,3,8 Since the appearance of distant lesions is exceptional, although the lesions have a high frequency of relapse, treatment with conservative surgery of the lesion has proved to be sufficient, and is therefore, the treatment of choice.1,16 However, on many occasions, we need to use an intermediate surgical option, such as partial cystectomy or partial nephrectomy.4,8 In pseudotumors with plenty of recurrence, or in those where their size impedes conservative surgery, we might consider an extended surgery (e.g. total segmental partial cystectomy). Radical excisional surgery with lymphadenectomy should not be considered in the treatment of these lesions.17

However, although no cases of tumor malignization have been reported in the literature, it seems advisable, given its nature and similarity with sarcomas, to carry out a strict follow-up, especially in cases with atypical histology.1,4,9–12 In conclusion, the urologist must know the entity of the inflammatory pseudotumor and properly evaluate its histopathology and immunohistochemistry. Only this way, we will be able to carry out an adequate intervention to prevent the performance of surgical overtreatment in the patients with this entity.

Conflict of interest

The authors declare that they have no conflict of interest.

References