CASE REPORT

Diffuse intestinal metaplasia of the urinary bladder causing bilateral hydronephrosis in a 48-year old man. A case report

George Tsamboukas¹, Vassilios Vossos¹, Ioannis Geramoutso¹, Panagiotis Politis¹, Gerasimos Vandoros³, Aristomenis Gekas¹

¹Department of Urology, General Hospital of Patras, Patras, Greece
²Department of Urology, General Hospital of Agrinion, Agrinion, Greece
³Department of Pathology, General Hospital of Patras, Patras, Greece

Abstract

Glandular cystitis is a benign disease of the urinary bladder, possibly caused by permanent irritation of urothelium by various causes. The atypical or intestinal morphological type of the disease intrigues as it has been hypothesized as a premalignant condition associated with bladder adenocarcinoma. Whereas such a relation remains controversial, severe sequelae can occur from the benign version of the disease, provoking dilemmas and making difficult its management by the urologist.

Introduction

Cystitis glandularis (CG) is a glandular metaplastic lesion of the bladder, commonly identified in normal organ specimens or at times in conjunction with urothelial or other carcinomas¹. The condition is the outcome of benign glandular differentiation in the von Brunn nests, while the cystic dilatation of these structures form the condition called cystitis cystica². Further metaplasia of the lining epithelium in mucin-filled goblet cells constitutes intestinal metaplasia (IM), a condition speculated as a precursor lesion for bladder adenocarcinoma (AD) by observation studies and case reports³, although other studies did not demonstrate such a connection¹. The irritation of the bladder mucosa in a persistent manner is the causative event, while the clinical spectrum of the condition is quite unspecific including hematuria, voiding symptoms or obstructive uropathy⁴. Since the condition can mimic radiographically and cystoscopically other malig-
nant lesions of the bladder, the usual management consists of transurethral resection of the mass and the disease is usually beatable, not needing further measures. However, persistent or complicated cases may demand more aggressive management. In this paper, we present a case of diffuse intestinal metaplasia of the bladder in a 48-year-old man. Moreover, the clinical significance of the finding, particularly in association with bladder AD, is discussed.

Case presentation
A 48-year-old man, of Slavian ancestry, was referred to our department by a nephrologist due to deterioration of serum urea and creatinine and imaging findings of bilateral upper tract obstructive uropathy. The patient referred no illnesses or drug intake and the general medical and urological history was unremarkable. No voiding symptoms or hematuria, during at least the last year, were reported. Ultrasonography showed bilateral upper tract obstruction with gross dilatation of both renal pelvises and ureters; moreover, the bladder wall showed manifold thickening and abnormal fattening of bladder trigone. Urine examination demonstrated mild pyuria, hematuria and the presence of mucus, while urine cytology was negative for malignancy. A non-contrast enhancement computer tomography was performed which sustained upper tract and ureters obstruction up to the ureteral orifices without obvious obstacle like lithiasis or tumor.

Due to the unknown nature of the mass in the bladder, the urologic team yield priority to the relief of the obstruction and the recovery of renal function. Bilateral percutaneous nephrostomy were placed and a diagnostic transurethral resection (TUR) of the lesion was then performed: cystoscopy revealed nodules-like structures lying underneath the submucosa, while ureteral orifices were undoable to be found. Biopsy specimens were taken from both the mass and from the healthy looking urothelium. The pathologic diagnosis was ‘cystitis glandularis with multifocal intestinal type metaplastic changes and focal mucosal ulceration’ (Figures 1, 2). A second, more aggressive, TUR was performed 3 weeks later for the establishment of the diagnosis, the total removal of the mass and for the deliverance of the orifices from the lesion. The pathologic report was identical (Figure 3).
One month later and since renal function had been recovered, a urogram via nephrostomies was performed. However, ureteral orifices were found still obstructed; moreover, repeat cystoscopy showed recurrence of the mass both in the trigone and in various sites. Because of the deterioration in patient’s life, the helplessness of the repeated TURs and the possible connection of IM with bladder adenocarcinoma, the patient was counseled undergoing ileal neobladder reconstruction in an expertise center. Indeed, the patient underwent the procedure, whom, to our dispatch, the pathologic report showed intestinal metaplasia in the ground of glandular cystitis of the bladder, without sign of malignancy.

Discussion

Cystitis glandularis is a metaplastic alteration of the urothelium, which can occur in both bladder and ureter\(^6\). The condition consists of two types of distinct morphology; the typical type is characterized by luminal structures within the lamina propria having an innermost lining of columnar or cuboidal cells and bounded peripherally by transitional cells, while the intestinal or atypical type, or intestinal metaplasia, has a similar architecture but contains mucin-secreting goblet cells in the lining epithelium\(^6\). Both types, especially IM, have been incriminated as premalignant conditions of bladder AD\(^7\). The histological differentiation of widespread IM from AD can be problematic, since both entities may secrete abundant extravasated stromal mucin; however, IM does not develop nuclear atypia or mitotic figures and rarely surpasses lamina propria, while classic signet ring cells and epithelial necrosis are not seen\(^5\).

Chronic inflammatory stimulation is considered the predisposing factor in the formation of CG\(^1\); bladder extrophy and pelvic lipomatosis\(^4\), chronic urinary tract infections, urolithiasis, intravesical drugs’ instillation, bladder outlet obstruction, neurogenic bladder and abdominal or pelvic radiotherapy\(^1\) have been reported as risk factors. Bladder trigone is the most common site of development and clinical spectrum is remarkable unspecific involving various lower urinary tract symptoms, hematuria or obstructive uropathy\(^7\). Cystoscopy or imaging studies cannot distinguish the condition from other malignant lesions and eventually the diagnosis cannot be made without microscopic examination\(^6\). Transurethral resection of the mass usually breaks the problem, but cases of persistent disease may require adjuvant intravesical BCG (bacillus Calmette-Guérin) or steroids instillations, while implication of the ureters may demand temporary percutaneous nephrostomy or further surgical intervention; ureteral reimplantation into the dome of the bladder or cystoprostatectomy with ileal neobladder reconstruction may be necessary\(^7\).

The most stimulating issue about IM is the possible premalignant role of the condition, as it has been implicated at a considerable number of case reports; the synchronous presence of bladder adenocarcinoma and diffuse CG or intestinal metaplasia in the specimens of most of these cases, provoked authors to classify the condition as precancerous\(^1\). More recent data from laboratories studies have attach importance to this hypothesis. Telomere shortening, already recognized in cancer development, has been found significantly present in urothelial intestinal metaplasia, while nuclear beta-catenin expression, a common signaling pathway with Barret’s metaplasia of oesophagus has been shown in intestinal metaplasia of the bladder and not it typical CG\(^6\). Cyclooxygenase - 2, an important enzyme regulating expression of the proto-oncogene bcl - 2 (b-cell lymphoma - 2), which inhibit apoptosis, has been found highly expressed in intestinal metaplasia and bladder adenocarcinoma tissues; the authors conclude that such over-expression likely contributes to sensitizing premalignant lesions to genotoxic carcinogens\(^3\). A transcription factor, called CDX - 2, nodal in the differentiation of intestinal epithelial cells, has been reported in a variety of adenocarcinomas and has been also observed in intestinal metaplasia but once again not in typical CG\(^6\). Another evidence of premalignancy that has been reported in both types of CG is considered the imbalance of the “guardian of the genome” TP53, a known antitumor - gene implicated in many kinds of cancer\(^6\). Finally, in their study, Gordetsky et al observed concurrent intestinal metaplasia with dysplasia and bladder adenocarcinoma in 40% of the cases, recommending close follow-up when dysplasia is apparent\(^6\).

In contradiction to these findings, cystitis glandularis is a relatively common finding in apparently healthy bladders in autopsy specimens\(^3\). Moreover, some studies have demonstrated negative association between CG, neither typical nor intestinal, and bladder adenocarcinoma. In the most extended study, Corica et al followed 53 patients...
Diffuse intestinal metaplasia of the urinary bladder causing bilateral hydronephrosis in a 48-year old man. A case report, p. 75-78

with intestinal metaplasia for a median time of more than 12 years and none of them developed cancer, and thus, authors concluded that IM is not a strong risk factor for the development of malignancy1. Two additional studies drew same conclusions after long-term tracking of 302 patients with typical or intestinal type of CG1,5. Given that conflicting data, the possibility of the premalignancy in bladder adenocarcinoma remains cloudy.

In conclusion, cystitis glandularis is a benign lesion of the bladder, which should always be concerned. Severe sequelae due to diffuse disease, especially of the intestinal type, like obstructive uropathy, may be remarkable and demand aggressive intervention. Of course, like in our case, we believe that such approaches should be considered the last hope. Finally, since recent research data alert the possible precancerous role of the condition, we strongly believe that the presence of IM, regardless dysplastic or not, should always alert urologists to keep these patients in close follow-up. 

Abbreviations
CG = Cystitis Glandularis
IM = Intestinal metaplasia
AD = Adenocarcinoma

References