Encrusting cystitis secondary to intravesical chemotherapy with mitomycin C

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ABSTRACT

Encrusting cystitis has been defined as an ulcerated inflammation of the bladder with calcium deposits in the bladder wall. It is an infrequent entity and can often go unnoticed. Identified precipitating factors are alkaline urine with pH above seven, previous bladder damage, urinary infection from ureolytic germs (Corynebacterium D2), and immunodepression. Previous bladder damage is not always demonstrable and it is necessary to rule out malignant process beforehand. Encrusting cystitis treatment includes three fundamental steps: Corynebacterium D2 infection control avoiding fluoroquinolones (76-83% resistance), urine acidification, and calcified plaque resection. The case of a sixty-two-year-old patient with past history of stage Ta papillary transitional cell carcinoma treated with transurethral resection of bladder tumor and intravesical chemotherapy with mitomycin C is presented, who nine months after bladder tumor resection developed calcium plaque adhered to the bladder mucosa at the previous resection site. Transurethral resection of bladder lesions was carried out and definitive histopathological study reported calcic crystal deposit with data of non-specific chronic cystitis resulting in diagnosis of encrusting cystitis.

RESUMEN

La cistitis incrustante se ha definido como una inflamación ulcerada de la vejiga con depósitos de calcio en su pared, es una entidad poco frecuente y que en muchas ocasiones puede pasar desapercibida; los factores precipitantes identificados son: orina alcalina con pH por encima de siete, existencia de daño vesical previo, infección urinaria por gérmenes de tipo urealítico (Corynebacterium D2) e inmunodepresión. La orina alcalina precipita las sales, que por su carácter ácido se alteran en este tipo de medio. El daño vesical previo no siempre es demostrable y es necesario descartar previamente un proceso maligno. El tratamiento de la cistitis incrustante enmarca tres pasos fundamentales: control de la infección por Corynebacterium D2 evitando las fluoroquinolonas (resistencia de 76% a 83%), acidificación de la orina y resección de placas calcificadas. Presentamos el caso de un paciente de 62 años de edad con antecedente de carcinoma papilar de células transicionales en estadio Ta, tratado con resección transuretral de tumor vesical y quimioterapia intravesical con mitomicina C, el cual desarrolló nueve meses después a la resección tumoral vesical placas de calcio adheridas a la mucosa vesical en el sitio de resección previa, realizándose resección

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INTRODUCTION

Encrusted cystitis has been defined as an ulcerated inflammation of the bladder with calcium deposits in the wall causing intolerable function and serious consequences for the patient. It is characterized from a functional perspective by the usual symptoms of cystitis and inconstantly by the elimination of encrusted crystals and even stones during micturition. Many factors are involved including the presence of a specific bacterium associated with alkaline urine, a preexisting urological procedure, or a preexisting mucosal lesion. A predisposing clinical context such as immunosuppression is an important cofactor. Urinary infection is due to the fact that bacteria convert urea into ammonia. Clinical findings are principally dysuria, urethral discomfort, and macroscopic hematuria. Urine contains mucus, pus, or blood, and has a strong smell of ammonia. Fever presents in 50% of cases. Bladder capacity is altered. There is a reduction in volume and finally retraction that reduces functional capacity.

Urinalysis presents with high urine pH, hematuria, pyuria, and struvite crystals. Urine culture is generally sterile and delays diagnosis even when there is irritative symptomatology. The fundamental purpose of intravesical chemotherapy is to eradicate existing disease, prevent recurrence, and prevent tumor progression. Mitomycin C is an antitumor antibiotic that induces changes in DNA composition. The induction of chemical cystitis has been observed after mitomycin C application. This is often an inflammatory response extending towards the depth of the bladder wall. After intravesical mitomycin C application the patient is exposed to urea-degrading bacteria and together with alkaline pH from the mitomycin C and damage to the bladder mucosa they create an environment conducive to the development of this entity.

CASE PRESENTATION

Patient is a 62-year-old man with a past history of smoking 20 cigarettes per day for 20 years. One year and four months prior to present illness patient presented with macroscopic hematuria. Patient was then diagnosed with transitional cell papillary carcinoma that was managed with transurethral resection of the bladder tumor. Tumor was stage Ta and so intravesical chemotherapy with mitomycin C was added. Present illness began with intermittent irritative symptomatology after finishing cycle of intravesical therapy with mitomycin C that was managed with fluoroquinolones with no symptom remission. Urinalysis reported pH of 7, leukocyturia, and microhematuria. Urine culture was sterile and remaining laboratory work-up was normal. Control cystoscopy was done that revealed an intravesical lesion at the previous tumor resection site (Figure 1). Study protocol was completed with excretory urography and computed axial tomography (CAT) (Figure 2) and transurethral resection of the intravesical lesion was programmed (Figure 3). During surgery, lesion was found to be completely adhered to the bladder wall making resection difficult. It had necrotic edges and a petrous consistency when cut. Partial resection of the lesion was carried out. Study of the surgical specimen reported calcic crystal deposit with non-specific chronic cystitis data. Concluding the diagnosis of cystitis incrustante secundaria a quimioterapia intravesical con mitomicina C.

Keywords: Encrusted cystitis, mitomycin C, transitional cell carcinoma of the bladder, intravesical chemotherapy, Mexico.

Palabras clave: Cistitis incrustante, mitomicina C, carcinoma vesical de células transicionales, quimioterapia intravesical, México.
DISCUSSION

In 1914 Francois described encrusted cystitis as a more or less localized ulcerated inflammation of the bladder wall with calcium phosphate deposits on the ulcerated surface and walls. This condition was studied in 1925 and 1926 by Hager and Magath and they concluded that it was the result of *B. proteus ammoniae* implantation in a bladder that is already the site of some sort of inflammatory or tumoral lesion. Encrusted cystitis is a severe inflammation of the bladder mucosa that requires a series of factors in order to be triggered. The fundamental factor for its existence is a precipitated salt deposit which requires alkaline urine. Currently *Corynebacterium group D2* is almost exclusively described in this disease and was demonstrated in 1985 by Soriano et al. This bacterium produces urease and releases large quantities of ammonium, modifying urine pH and turning it markedly alkaline. The infected urine becomes saturated with struvite and calcium phosphate that can precipitate in an adequate bladder area, resulting in bladder wall encrustations. Bladder encrustations require a preexisting lesion in the urinary tract mucosa that is often secondary to urological procedure.

The urinary bladder can have a complex set of reactions to various damaging stimuli such as prolonged inflammation caused by *Corynebacterium uraliticum*.

Smooth muscle cells, myofibroblasts, vascular calcification cells, and microvascular pericyte cells can exhibit pathological phenotypic changes under certain conditions such as prolonged inflammation. There has been speculation that strong alkaline pH and the presence of cellular fragments derived from apoptotic cells constitute the environmental conditions that favor calcium phosphate precipitation. This germ requires specific determinations for its isolation since it is opportunistic and largely nosocomial. Mitomycin C as a bladder chemotherapeutic agent after endoscopic resection, while not being able to be established as the direct causal agent of encrusted cystitis, its action at the bladder mucosal level, its pharmacological characteristics, its tendency to alkaline pH, and the necessity of repeat catheterization for its administration do make it a potentially contaminating urinary agent that can be an important factor in the development of the disease.

Encrusted cystitis is a chronic disease with long-lasting symptoms and its first description is still valid: “Encrusted cystitis is typified, from a functional point of view, by habitual cystitis characteristics, but inconstantly, by the elimination of incrustation and even stone residuals.”

In the case of encrusted cystitis, bladder wall deterioration and calcifications can induce pyelocaliceal dilatation and progressive kidney function deterioration. Bladder adaptability can also be altered by volume reduction, finally resulting in retraction and complete loss of functional capacity.
Radiographically visible calcification of the bladder wall after cystitis has been extremely rare since the advent of antibiotics. Excretory urography in cases of encrusted cystitis reveals a calcified margin that is noted in the bladder and prostate, with secondary pyelocaliceal dilatation on a piriform bladder with irregular margins.

Ultrasound is sensitive for encrusted cystitis diagnosis and shows thickening and calcified lesions in the bladder wall and possible upper urinary tract dilatation. It is a successful diagnostic tool when calcifications can be visualized in the urothelium and not in the opening of the urinary tract.

Computed tomography (CT) that is carried out to detect high density in the edges of urinary tract lesions shows calcifications associated with important edema. In the bladder this appears to be an optimum technique for encrustation diagnosis since it is more encrustation sensitive, even when encrustations are thin and radiolucent in radiographs. It provides excellent visualization of the urothelial wall and calcification. These calcifications that superficially cover the urothelium can be fine and regular. Contrast medium injection is not necessary for diagnosis. CT is also carried out for lesion follow-up after adequate treatment. Direct vision examination of encrusted cystitis reveals marked inflammatory appearance of all or part of the bladder mucosa with ulcerations and whitish plaque corresponding to multiple calcified encrustations.

These encrustations vary in size from a wooly fragment lying in the mucosa to actual calcified plaque deeply encrusted in the bladder wall. The preferred zones for these encrustations are the trigone, the ureter, the bladder neck, and previous sites of endoscopic resection, surrounded by bright red edematous and hemorrhagic mucosa. Encrusted cystitis treatment consists of three complementary elements: treatment of infection, urine acidification and chemolysis, and elimination of calcified plaque that contains microorganisms. The discovery of new antimicrobial agents has transformed the results of these infectious diseases. All Corynebacterium group D2 strains are sensitive in vitro to glycopeptides, vancomycin, and teicoplanin and have a similar effect. Sensitivity has been maintained constant since the first description of bacteria associated with encrusted cystitis. Corynebacterium group D2 sensitivity to fluoroquinolones is irregular and resistance rates are at times higher than 50%.

Calcified plaque contains high levels of microorganisms and limits in vivo antibiotic effectiveness. Surgical or endoscopic plaque removal is suggested. Transurethral resection of bladder plaque remains difficult with risk of segment rupture.

Bladder wall healing depends on calcium precipitation prevention and therefore on the prevention of calcium salt oversaturation in alkaline urine. Two types of treatment for inducing urine acidification are oral urease inhibitors or direct topical acidification.

**CONCLUSIONS**

Encrusted cystitis is a severe inflammation of the bladder mucosa that requires a series of factors for its development. The fundamental factor is salt precipitation deposit leading to alkaline urine. A final urine pH of 7 and 8 after mitomycin C instillations has been documented.
In the present case it was not possible to identify the presence of urinary germs in any of the determinations. However, repeated catheterization for mitomycin instillations was an important urinary contamination factor.

The development of encrusted cystitis is produced in the majority of reported cases from a background of bladder lesions. In the present case the lesion was very clear. On the one hand there was the wound from the endoscopic resection and on the other was the mucosal inflammation caused by mitomycin C that is inherent in its cytostatic action. In regard to treatment it has been shown that urinary acidification is sufficient to resolve the process, together with the addition of existing plaque resection and the achieving of urine sterilization.

BIBLIOGRAPHY