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Review article

Iatrogenic pathology of the urinary bladder

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ABSTRACT

Intravesical immunotherapy, chemotherapy, and neoadjuvant systemic chemotherapy are among the most frequent therapeutic procedures to treat malignancies of the urinary bladder. These treatment modalities produce reactive morphologic changes in the urothelium that can mimic urothelial carcinoma in situ, urothelial dysplasia or true invasive urothelial neoplasia. Mitomycin C used after transurethral resection of bladder tumor to reduce recurrences, BCG intravesical immunotherapy to treat high risk non-muscle invasive bladder cancer and urothelial carcinoma in situ, and platinum-based systemic chemotherapy to improve post-cystectomy disease-specific survival some of the causes of therapy related atypia in urinary bladder. In addition, a number of systemic drugs in use to treat other systemic diseases, such as cyclophosphamide used to treat certain autoimmune disorders or hematologic malignancies, or the anesthetics ketamine increasingly used as illegal recreational drug, may produce similarly relevant atypical changes in the urothelium, and therefore, need to be differentiated from intraepithelial neoplasia. Immunohistochemical approach to reactive urothelium from CIS using CK20, p53, and CD44 may also be of utility in the pos-therapy scenario.

Introduction

About 70% of newly diagnosed urothelial bladder cancer cases are classified as non-muscle-invasive (NMIBC) which includes Ta (non-invasive) and T1 (subepithelial connective tissue invasion) tumors and carcinoma in situ (CIS).[1] Urothelial carcinomas of the bladder are frequently treated by a combination of surgery, intravesical immunotherapy, chemotherapy or radiation-therapy using specific pathology-based protocols, mostly grade and stage.[2–86] For instance, intravesical Mitomycin C to reduce tumor's recurrences or intravesical BCG (Bacillus Calmette-Guerin) immunotherapy will follow the diagnosis of high grade non-muscle invasive bladder tumor in addition to transurethral resection of the bladder tumor. According to current guidelines, these patients receive frequent cystoscopies with mapping biopsies to evaluate therapeutic efficacy or to diagnose potential urothelial alterations.[2] The level of cellular atypia may simulate intraepithelial neoplasia, or may represent areas of true residual neoplastic disease.[18] The pathologist should keep in mind that pos-therapeutic diagnosis of residual and recurrent bladder cancer is a great challenge.[2,12] Alternative therapeutic approaches, such as gene therapy or different forms of immunotherapy alone or in different combinations with chemotherapy have been recently adopted although remain as experimental procedures.[2–12]

Neoadjuvant systemic platinum-based chemotherapy is increasingly applied in most institutions before surgery in an attempt to improve cancer specific survival.[42–47] However, there is limited data on tissue and cellular changes related to this therapy, both in the tumor itself and the non-neoplastic urothelium.[2–20]

The aim of this paper is to review the morphologic urothelial changes induced by traditional and novel therapeutic procedures in use to treat bladder urothelial cancer and to provide morphologic and immunohistochemical clues that may be useful in resolving difficult differential diagnoses that could be encountered in such settings. Changes induced by systemic chemotherapy in the urothelium are also presented. The following intravesical, local and systemic therapeutic procedures are reviewed:

- Chemotherapy
- Immunotherapy
- Radiation Therapy

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- Surgery
- Photodynamic and laser therapy
- Gene therapy
- Other therapy related alterations

Chemotherapy

Chemotherapeutic agents frequently used either intravesically or systemically, may produce urothelial reactive atypical changes that occasionally might be mistaken for urothelial carcinoma in situ.[2–32]

Intravesical chemotherapy

Intravesical therapy is applied in order to eradicate existing disease, to prevent tumor recurrences, and to prevent tumor progression.[6,12–16] Nowadays, the main goal for intravesical chemotherapy is to limit the number of recurrences after TUR of bladder tumor, most frequently by bladder instillations of mitomycin C after resection.[6,12–16]

Mitomycin C

Mitomycin C is currently the most frequent intravesical chemotherapeutic agent in use. It is an antitumor antibiotic which induces inter and intra-strand cross links in DNA molecules. It has been shown to degrade DNA and inhibit its synthesis, thus making it effective during the late G1 and S phases of the cell cycle Table 1.[6,12–16]

Mitomycin C produces histologic and cytologic alterations in normal urothelium including cellular exfoliation, denudation, and atypical changes in the superficial umbrella cells.[2–16] Such cells become large, vacuolated and often multinucleated with small nucleoli. The cellular alterations are not specific and may also be caused by chronic irritation due to inflammation, catheterization, and instillation of saline solutions. These atypical cells can persist in cytologic specimens for a variable period after discontinuation of therapy. Less significant abnormalities may be seen in the deeper layers of the urothelium. Limited data suggest that immunohistochemical expression of p53, CD44, and CK20 in this setting is similar to what is seen in reactive urothelium. Furthermore, AMACR is frequently negative in reactive atypia in the post-therapy setting thus suggesting a role of AMACR in combination with p53, CD44 and CK20 in differentiating reactive atypia vs. CIS after therapy.[59–61]

A hemorrhagic and necro-inflammatory process similar to chemical cystitis follows intravesical administration of mitomycin C. There is often a histiocytic response that extends deep into the bladder wall with isolated single and clustered macrophages. Mitomycin C may also initiate an eosinophilic cystitis. Fibrosis with scarring and bladder wall calcification has been documented in rare cases after long-term topical therapy Fig. 1.[2–16]

In case of persistent papillary neoplasia, Mitomycin C suppresses tumor growth and limit progression, but does not eradicate cancer. It is thought to act as surface abrasive to destroy the tips of papillary fronds, resulting in stubby papillae lined by neoplastic cells or fully denuded papillae. Urothelial denudation makes recurrences difficult to detect cystoscopically and document histologically but urothelial dysplasia and carcinoma in situ have been found in von Brunn's nests in case of residual disease.[12–16]

Table 1
Pathologic features associated with mitomycin C intravesical chemotherapy.

Atypia in the surface umbrella urothelial cells
Denudation of the surface epithelium
Less significant abnormalities in the deeper layers of the urothelium
Denuding papillae of persistent papillary neoplasia
Associated eosinophilic cystitis (mild-to-moderate; common)
Low nuclear/cytoplasmic ratio
Hemorrhagic cystitis (rare)
Encrusted cystitis (rare)

Other topical agents

A range of other intravesical chemotherapeutic agents remain useful in selected patients. Thiotepa (triethylenethiophosphoramide), an alkylating agent, is the oldest of the intravesical chemotherapeutic agents still in use. Its mechanism of action involves the formation of covalent bonds between DNA /RNA and proteins which thus results in nucleic acid synthesis inhibition. Thiotepa also reduces cell adherence with a direct cytotoxic effect.[14] Thiotepa and Mitomycin C produce identical histologic and cytologic alterations in the normal urothelium and the bladder wall.[12–16]

Doxorubicin (Adriamycin), epirubicin, valrubicin, ethoglucid (epodyl), cisplatin and mitoxantrone are known to cause alterations in the bladder mucosa.[2–16] The frequency varies from agent to agent. For example, there is a 21 to 25% incidence of epirubicin and doxorubicin-induced cystitis, respectively. Cystitis ranging from 3–56% has been seen with ethoglucid. Gemcitabine, a pyrimidine analog with a broad spectrum of antitumor activity is gaining activity as second line intravesical chemotherapy agent.[2–16]

The full morphologic description of the changes in the urothelium and in the lesions being treated specific to these agents is not available, but limited data from our experience suggest pathologic alterations similar to the changes described for mitomycin C and Thiotepa.

Systemic chemotherapy

Several agents are systemically administered to treat different neoplastic and non-neoplastic disorders. Among these agents, cyclophosphamide is known to severely affect the urothelium. Other agents as ketamine are increasingly used as illegal recreational drug may produce ketamine cystitis with severe changes in the urothelium with potential to mimic of urothelial CIS.[17–34] Neoadjuvant systemic platinum-based chemotherapy is increasingly applied before cystectomy in attempt to improve cancer specific survival. The pathologists is increasingly asked to evaluate the efficacy of such treatment and recognize the reactive lesions that could be associated Table 2.

Cyclophosphamide

Cyclophosphamide is an alkylating agent used to treat a variety of malignancies including lymphoproliferative disorders, as well as diseases such as systemic lupus erythematosus, rheumatoid arthritis, organ transplantation, or nephrotic syndrome.[17–34] Active metabolites, acrolein and phosphoramide concentrate in the urine and thus be in contact with the urothelium. The drug is a toxic to the urinary bladder that increases the risk for urinary bladder cancer for years after therapy.[17–34] Cyclophosphamide causes cell division arrest that results in large, bi-or-multinucleated cells often with bizarre nuclei resembling changes of radiation injury mimicking intraepithelial neoplasia. There is marked but variable cellular and nuclear enlargement. Nuclei are usually hyperchromatic, often eccentric with slightly irregular outlines. Nuclear pyknosis is a common late effect that results in loss of chromatin texture. Chromatin may be coarse but is usually evenly distributed. Nucleoli are single or double and are occasionally large and distorted with irregular and sharp edges. These architectural and cellular abnormalities of the urothelial cells may be mistaken for malignancy.[17–34]

Systemic cyclophosphamide therapy typically induces hemorrhagic cystitis.[17–34] Histology also include vascular ectasia, severe edema, and hemorrhage of the lamina propria, usually associated with necrosis of the epithelial lining and mucosal ulceration covered with fibrinopurulent exudate. In our experience, immunohistochemical expression of p53 and Ki67 is low, and CK20 is expressed in superficial cells of the urothelium, therefore supporting the reactive nature of the