Radiation-induced epithelial proliferation mimicking invasive carcinoma of the urinary bladder
– A Report of 2 Cases –

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Therapeutic radiation in patients with carcinoma of the uterine cervix or rectum may induce a variety of pathological changes in the urinary bladder. Radiation cystitis, either acute or chronic, is very common when the bladder is included in the treatment field. Radiation induces cyto logic atypia in both epithelial and mesenchymal cells, which closely mimic and are sometimes indistinguishable from in situ carcinoma of the urinary bladder on hematoxylin-eosin stained sections.1 However, although rare, a striking epithelial proliferation, coupled with cytologic atypia, can cause problems in the differential diagnosis of invasive carcinoma.2 In this paper, we describe two cases of radiation-induced epithelial proliferation mimicking invasive urothelial carcinoma in patients receiving radiation treatment for cervical carcinoma.

CASE REPORT

The first patient was a 44 year-old woman, who had undergone a cystoscopy for work-up under the suspicion of recurrent uterine cervical cancer. Twenty one months previously, the patient had received a concurrent chemoradiotherapy with an external beam and an intracavitary irradiation (84 Gy) and cisplatin-based chemotherapy due to FIGO stage IIIb cervical cancer. The cystoscopic finding revealed bullous or edematous mucosal changes with multiple hemorrhagic foci. Microscopically, we observed inverted epithelial proliferation, forming nests and cords extending into the lamina propria. The epithelial cells in these nests and cords exhibited enlarged, hyperchromatic and pleomorphic nuclei, closely mimicking the infiltrative growth of urothelial carcinoma. However, the presence of radiation-induced changes was validated by the observation of abundant vacuolated cytoplasm, normal or slightly increased nuclear to cytoplasmic ratios, the absence of mitotic activity, dilated blood vessels containing frequent fibrin thrombi, scattered atypical fibroblasts, and the patients’ previous history of radiation treatment. Radiation-induced changes should be always included in differential diagnoses of proliferative epithelial lesions in the urinary bladder and a pertinent clinical history of radiotherapy should be searched.

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ited a few foci of inverted epithelial proliferation, extending into the lamina propria. These manifested as nests and cords, and closely mimicked the infiltrative growth of urothelial carcinoma (Fig. 1). The boundaries of the nests and cords were irregular and jagged. Epithelial cells in the nests and cords exhibited large, hyperchromatic and often smudged nuclei with abundant vacuolated cytoplasm (Fig. 2). The nuclear to cytoplasmic ratio was not increased. Nucleoli were absent or inconspicuous, and no mitoses were identified. In case 1, the adjacent urothelium was mostly flat, and composed of a maximum of 6 layers of epithelial cells, displaying nuclear atypia and mimicking urothelial carcinoma in situ, but the polarity was relatively well preserved in this case and no mitotic activity was identified (Fig. 3). In case 2, the cell nests in the lamina propria resembled inverted papilloma without exophytic components, and small clusters of cells or single cells were observed around the nests (Fig. 4). The stroma was partly edematous and partly fibrotic with moderate infiltrations of inflammatory cells, extravasated RBCs, hemosiderin depositions, and dilated vascular channels frequently containing fibrin clots (Fig. 5). In both cases, there were scattered atypical fibroblasts in the lamina propria (Fig. 6).

**DISCUSSION**

With the increasing use of radiation therapy for the treatment of variety tumors, we have become increasingly aware of the complications and histologic changes sometimes associated with radiation. Immediately after the radiation, rapidly dividing epithelial cells are more susceptible to the radiation damage compared to the slowly growing cells, such as endothelial cells. The early signs...
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of acute radiation cystitis typically present as vascular damage, which may appear immediately after a course of radiation therapy. Acute radiation cystitis occurs in 2% to 4% of the patients who undergo radiation for pelvic neoplasms, but the incidence of this complication is dependant on the dose and field of the employed radiation. The incidence of acute radiation cystitis is higher in patients who have undergone radiotherapy for bladder cancer than in those who have undergone radiotherapy for cervical or rectal cancer. The fibroblasts demonstrate the evidence of radiation damage in the later and the late reactions may appear at any time, even months or years after the completion of treatment. Radiotherapy may cause progressive fibrosis resulting in ulcers, cicatricial contraction of the bladder, and secondary ureteritis with ureteral obstruction or strictures.

Microscopically, the early radiation induced changes in the bladder are characterized by marked edema and hyperemia in the lamina propria and the subsequent desquamation and superficial ulceration of the urothelium. This edema induces a thickening of the mucosal folds, resulting in a characteristic gross appearance. The urothelium may also display atypical cytologic features mimicking and sometimes indistinguishable from transitional cell carcinoma in situ (TCIS), although mitotic activity is very rare in these cases. The cells may exhibit enlarged, hyperchromatic nuclei, which appear more bizarre than those of TCIS. They are characterized by multinucleated, vacuolated and degenerative appearing nuclei. Occasionally, pseudoinfiltrative growth with cords and nests extending into the lamina propria can be seen as in our cases, and therefore they create a diagnostic confusion, appearing to be invasive carcinoma.

Chronic radiation induced changes include the collagenization of the lamina propria, myointimal proliferation or hyalinization of the arterioles, and ulceration with abundant fibrinous exudates on the mucosa. Atypical fibroblasts are invariably scattered throughout the lamina propria. The urothelium may be either atrophic or hyperplastic, may undergo squamous metaplasia, and may still exhibit focal radiation-induced atypia. These late changes may persist for years or permanently, or heal very slowly. Despite the fact that epithelial changes are usually observed in early lesions and stromal changes in late lesions, there is a continuous spectrum of epithelial damage which persists for many years after the initial radiation. Epithelial damages, as evidenced by cytoplasmic vacuolation and cell proliferation, may also be present in late lesions, as they were in our second case. These features may be a result of continuous damage to the epithelium even after the acute ulcers have healed or may represent radiation-induced genetic damage to the surviving epithelial cells.

When the atypical nuclear changes in the urothelium are not associated with an overall loss of polarity or high nuclear to cytoplasmic ratio, and when the cells with multinucleated or smudged nuclei and basophilic or vacuolated cytoplasm are not associated with mitotic activity, the possibility of radiation induced changes should always be raised. Other helpful features include scattered atypical stromal cells and vascular changes.

In the histologic evaluation of proliferative epithelial lesions of the urinary bladder, it is important to consider the possibility of radiation damages in order to avoid erroneous diagnosis of malignant tumor, even when information regarding the patient’s clinical history is unavailable.

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