CIS of the bladder: a review of literature

Mesanede karsinoma in situ: literatür derlemesi

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ABSTRACT

Carcinoma in situ (CIS) of the bladder poses a clinical challenge to urologists worldwide. The clinical course of CIS ranges from benign, indolent tumor growth to highly progressive tumor proliferation with deleterious effects on patient outcome and increased disease-specific mortality. The aim of our review was to outline the natural history of bladder CIS in a single concise source for young urologists. We performed a PubMed review of the literature on CIS of the bladder. We used CIS, BCG and superficial bladder cancer as the keywords for our search. Following a group discussion, the authors selected 77 important publications to be included in our review article. The presence of bladder CIS increases the risk of panurothelial disease involving the prostate, urethra or upper urinary tracts. Urine cytology is the primary approach for the diagnosis of CIS. Intravesical BCG remains the gold standard for the initial treatment of CIS. Early radical cystectomy for cases that present BCG failure showed a higher rate of success with long-term cure. Frozen section biopsy of the distal ureter should be performed when CIS of the bladder has been preoperatively diagnosed. Whether frozen section biopsy was performed and regardless of the condition of the distal ureter at the time of cystectomy, postoperative follow-up with cytology, endoscopy of the new pouch and ureteroscopy of the ureters is recommended for early detection of possible recurrence.

Key words: BCG; carcinoma in situ; intravesical chemotherapy

ÖZET

Mesanede karsinoma in situ (KIS) tüm dünyada ürologlar için bir klinik sorun oluşturmaktadır. Tembel bir tümörden, hastanın akibeti üzerine zararlı etki ve hastalığa özgü mortalite artışı ile birlikte oldukça progresif bir tümöre kadar değişen geniş bir klinik seyre sahiptir. Derlememizin amacı genç ürologların mesane KIS'in doğal seyrini anlamaları için özet bir kaynak sağlamaktır. Mesane KIS çalışılan literatürlerin bir pubmed derlemesini yaptık. Tarama sırasında anahtar sözcükler olarak "CIS", "BCG" ve "superficial bladder cancer" kullandık. Grup tartışmasını takiben, yazarlar 77 önemli yayının derleme makalemize dahil edilmesine karar verdi. Mesane KIS mevcudiyeti prostat, uretra veya üst idrar yollarını tutan panurotelial hastalık riskini artırmaktadır. İdrar sitolojisi KIS tanısı için başlıca dayanaktır. İntravezikal BCG KIS başlangıç tedavisi için altın standart olmayı sürdürmektedir. BCG'nin başarısız olduğu olgular için erken radikal sistektomi uzun dönemli kür oranları ile daha yüksek başarı göstermiştir. Mesanede KIS tanısı ameliyat öncesi konulduğunda, distal ureterin (frozen section) biyopsisi yapılmalıdır. Sistektomi sırasında distal ureterin durumuna veya frozen kesit yapılıp yapılmadığına bakılmaksızın, olası rekürrensin erken saptanması için sitoloji, yeni kesenin endoskopisi ve ureterlerin ureteroskopisi ile ameliyat sonrası takip önerilmektedir.

Anahtar sözcükler: BCG; karsinoma in situ; intravezikal kemoterapi

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Introduction

Definition

Carcinoma in situ (CIS) is defined as flat (non-papillary), high-grade and involving either the entire thickness or part of the urothelium.[1]

Using the 2002 TNM classification system, CIS is classified, together with Ta and T1 papillary tumors, as superficial tumors of the bladder.[2]

Historical review

CIS of the bladder was first described in 1952 by Melicow, who evaluated grossly normal appearing mucosa of tumor-bearing bladders, identified foci of cellular activity and diagnosed the foci as malignant with invasive potential, rather than precancerous lesions.[3,4]

The 1998 WHO/ International Society of Urological Pathology consensus expanded the

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definition of CIS to include lesions previously designated as severe dysplasia or marked atypia.[5]

Risk of CIS

The natural history indicates a greater than 50% 5-year progression rate to invasive disease and higher recurrence rate.[6,7] If CIS is associated with T1 papillary tumor of the bladder, the progression rate increases to 80% for cases treated by resection only (TURBT).[8] CIS of the bladder is associated with a 3- 4-fold higher risk for CIS of the upper urinary tract (UUT) than invasive bladder tumors.[9,10]

Salsona et al.[11] reported that in patients undergoing cystectomy, the incidence of UUT TCC was higher among cases with bladder CIS (8 of 46, 17.4%) than among cases with invasive bladder cancer (7 of 179, 3.9%) ($p<0.01$).

Wang et al.[12] compared UUT TCC recurrence rates after primary invasive bladder cancer with those after CIS and identified a higher incidence after CIS. The incidence of UUT TCC recurrence after CIS of the bladder was 11 out of 56 (19.6%), whereas following invasive bladder tumor, the incidence was 11 out of 420 (2.6%) (p-value=0.007).

Nixon et al.[13] reviewed 192 consecutive radical cystectomy specimens and noted that in specimens from patients with CIS in the bladder, 31.3% had prostatic urethral involvement. The authors concluded that the risk of prostatic urethral involvement is 12-15-fold higher when CIS or multifocality of bladder urothelial carcinoma is present.

Iba et al.[14] published a case report of CIS of the bladder neck, which invaded the prostatic stroma and was difficult to diagnose, except by TRUS-guided biopsy.

Millan et al.[10] detected that out of 1529 patients who underwent random biopsy of the bladder and prostatic urethra, 19% had CIS of the bladder and 2.7% had CIS of the prostatic urethra.

In contrast to testicular CIS and prostatic intraepithelial neoplasia, CIS of the bladder is a dangerous disease with a narrow window between successful treatment and progression or even disease-specific mortality. Shariat et al.[15] demonstrated 3-year bladder cancer-specific survival rates of 65% and 37% for patients with de novo invasive tumor and patients with tumor progression beyond the CIS criteria, respectively.

Schrier et al.[16] demonstrated that patients experiencing disease progression from CIS to muscle-invasive tumors have a significantly worse prognosis compared with stage- and age-matched patients with de novo invasive tumors.

Masood et al.[17] demonstrated that 55% of patients with clinically high grade T1 bladder cancer and concomitant CIS experienced upstaging at cystectomy compared with only 6% of patients with clinically high grade T1 of the bladder without CIS.

Focal CIS may exist for years and progresses in as few as 8% of patients.[7]

Incidence

Primary CIS constitutes 1-3% of all urothelial neoplasms.[1] Secondary CIS is detected during follow-up in 90% of cases with urothelial neoplasms.[7]

Also, 45-65% of invasive urothelial carcinoma and 7-15% of superficial papillary carcinoma are accompanied by CIS.[1]

CIS is noted predominantly in male smokers in the sixth and seventh decades of life.[18]

Kaasinen et al.[19] reported that 5% of patients with superficial bladder cancer had concurrent CIS. Palou et al.[20] reported a 19% incidence of concurrent CIS.

Clinical types

According to Lamm et al.,[21] bladder CIS can be classified into 3 clinical types:

1. Primary CIS: isolated CIS with no previous or concurrent papillary tumor
2. Secondary CIS: CIS detected during the follow-up of patients with a previous papillary tumor
3. Concurrent CIS: CIS in association with a papillary tumor

Genetic changes

There are several genetic changes that may predispose patients to develop CIS of the bladder and allow disease progression to invasive bladder tumor growth.

The most important genetic changes are deletion/ mutation of the P53 gene located on 17p13.1, loss of cyclin-dependent kinase inhibitor (CDKN2/p16) and deletion of 9q.[22-24]

Clinical presentations

CIS presents with irritative bladder symptoms in the form of dysuria, frequency and urgency. Hematuria, if present, is typically microscopic.[1,25]

Diagnosis

1) **Urine cytology:** CIS is associated with loss of cell cohesion in the epithelial lining of the bladder; therefore, a large number of floating cells are found in urine. Therefore, CIS is nearly always detected by urine cytology with a sensitivity and specificity of over 90%. Cytology can be performed

on voided urine or bladder wash (barbotage) during cystoscopy; however, the EAU guidelines recommend performing cytology on voided urine, unless a bladder wash is performed at the time of cystoscopy.[26] The recent European guidelines insist on performing cytology on fresh urine with adequate fixation and also state that morning urine is unsuitable because cytolysis may be present.[27] Cellular anaplasia, loss of polarity, discohesion, nuclear enlargement, hyperchromasia, pleomorphism and atypical mitoses are the histopathological hallmarks of CIS.[18]

However; Sharkey[28] found a considerable discrepancy between local and review pathology, in which 22% of the cases with CIS were downgraded to dysplasia, whereas 30% of the reports of dysplasia were upgraded to CIS.

Yin et al.[29] suggested that the combined use of cytokeratin 20 (CK20) and Ki-67 is sufficient to allow discrimination of CIS from dysplastic cells.

2) **Urine markers:** Over the last decade, many markers became available to aid in CIS diagnosis and its discrimination from urothelial dysplasia. Schwarts et al.[30] and Nese et al.[18] demonstrated the promising role of UroVysion fluorescent in situ hybridization (FISH) in clearly differentiating patients with CIS from patients with dysplasia or reactive atypia; detecting polysomic cells (of chromosomes 3, 7 and 17) and deletion of the 9p chromosome, which are particularly present in CIS and invasive urothelial tumors. Kageyama et al.[31] reported the high sensitivity of calreticulin (CRT) in detecting bladder cancer cells, but CRT has low specificity.

   Sullivan et al.[32] reported a higher sensitivity of ImmunoCyte compared with both urine cytology and UroVysion in detecting bladder cancer but a lower specificity; the specificity was 97%, 63% and 90% for urine cytology, ImmunoCyte and UroVysion, respectively. Mian et al.[33] confirmed the particularly high sensitivity of ImmunoCyte in detecting CIS of the bladder and concluded that combining both cytology and ImmunoCyte can detect 100% of cases with bladder CIS during follow-up of bladder cancer patients. Shariat et al.[34] incorporated nuclear matrix protein 22 (NMP22) in a nomogram to predict disease recurrence and progression in patients with Ta, T1 or CIS of the bladder.

3) **Standard (white light; WL) cystoscopy:** This method may reveal no visible abnormalities, edema of the wall or red velvet-like patches. Witjes[35] concluded that cystoscopic diagnosis of CIS with WL cystoscopy is not optimal and can miss many cases. In a European multicenter study,[36] only 58% of all CIS lesions were detected with WL cystoscopy. Considering the optimal conditions of such a study (high-risk patients and trained investigators), the number of undetected cases can be even higher in normal daily practice. Zaak et al.[37] found that WL cystoscopy failed to detect 53% of specimens with CIS.

   Uchikoba et al.[38] reported a new technique for improving the detection of CIS with WL cystoscopy, which involved instillation of pirarubicine hydrochloride into the bladder. After 5 minutes, the bladder was examined using WL cystoscopy, and increased uptake was clearly noted in cases of CIS. However, the authors noted false positive results due to increased uptake, as well as for cases with urothelial hyperplasia.

4) **Fluorescence cystoscopy:** This procedure is used to reveal areas in the bladder that are suspicious for CIS and undetected by WL cystoscopy, and it improves the detection of CIS to more than 95%.[26,36,39] The feasibility and superiority of photodynamic diagnosis (PDD) using 5 aminolevulinic acid (5-ALA) over WL cystoscopy for the diagnosis of CIS has been well-documented.[37,40-42] A recognized limitation to PDD cystoscopy is the increased rate of false positive patients compared with WL cystoscopy, especially for cases with chronic bladder inflammation and post instillation of chemotherapy into the bladder. However, Colombo et al.[43] demonstrated improved detection of CIS compared with WL cystoscopy during follow-up of patients on BCG instillation therapy. In addition, the higher cost of the initial use of PDD cystoscopy for cases with bladder tumor has been considered. A group from Germany studied that issue over a series of 301 patients and concluded that PDD significantly cut costs related to recurring cystoscopy.[44] Thus, although PDD can be more expensive for an initial diagnosis, PDD can still be cost-effective because of the lower recurrence rate and the lower rate of follow-up cystoscopy and resection of bladder tumors. Another group from Sweden studied the budget impact of using HAL combined with WL cystoscopy for the management of bladder cancer and concluded that the combination may reduce invasive, time-intensive and high-cost procedures, such as cystectomy and TURB, compared with WLC alone.[45] Inoue et al.[46] confirmed mild bladder irritability and absence of systemic side effects from applying PDD, and the authors recommended that PDD be used as the gold standard for the detection of bladder tumors.

5) **Bladder biopsy:** European guidelines have recommended that whenever positive cytology is present, random biopsies should be taken from the bladder and prostatic urethra, and a bladder diagram should be used to identify the exact location of the biopsied areas.[26]

   In a recent study, a Japanese group detected 11.8% cases with CIS in intermediate and high-risk cancer cases without abnormal cystoscopy and positive cytology. Because of this finding, they recommended routine random biopsies from normal looking sites whenever there is positive cytology, regardless of the cystoscopic findings.[47] Either cold cup biopsies or resection loop can be used to take the random biopsies, and it is advised that the biopsies be sent for assessment in separate containers.[45]

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6) **Upper tracts studies:** Whenever positive cytology is detected along with an absence of visible tumor on cystoscopy and IVU and normal biopsies from the bladder and prostatic urethra, CIS in the upper urinary tracts should be suspected.[11] Diagnosis of the affected renal unit can be made by selective cytology using a ureteral catheter in combination with ureteroscopy and brush sampling.[26]

Treatment

1) **Intravesical chemotherapy:** Lamm [21] reported that intravesical chemotherapy produced a complete response rate of 38% in patients treated with Thiotipa, 48% in patients treated with doxorubicine and 53% in patients treated with mitomycin C. Sylvester et al.[48] demonstrated that no single drug has superior efficacy compared with the others, and all have a beneficial effect when given as an adjuvant single instillation following transurethral resection of the bladder tumor (TURBT). However, in the study by Sylvester, all patients with high-risk bladder tumors were included whether they had CIS or not. Conversely, in another study by the same group, mitomycin C was superior to other chemotherapeutic agents in treating CIS with no superior effect on Ta and T1 lesions.[49] Severe complications have been reported in cases of drug extravasation.[50] Therefore, EAU guidelines[27] recommend omitting the immediate instillation of chemotherapy in cases of extensive TUR procedures, which are suspicious for intra- or extra-peritoneal perforation. Campodonico et al.[51] considered Gemcitabine to be the best drug for single instillation following TURBT. Whatever the drug used, it should be diluted in sterile water and not saline, and the highest efficacy is achieved when administered within 6 hours post-resection. Sylvester[48] showed that the best results can still be achieved with delayed instillation for up to 24 hours. EAU guidelines[27] recommend using the drug at its optimal pH and to maintain the concentration of the drug by decreasing fluid intake. The optimal schedule and duration of treatment is unclear, but it should be maintained for 6-12 months. Intravesical chemotherapy acts by decreasing recurrence with no effect on tumor progression.[52] The results from using intravesical chemotherapy, however, remains unpromising. Valrubicin is the only FDA-approved drug for patients with CIS; it showed a 21% and 8% complete response after 1 and 2 years, respectively.[53] Dalbagni et al.[54] demonstrated a complete response of 21% after 1 year of applying intravesical Gemcitabine for CIS cases. A recent paper[55] studied the effect of a combination of intravesical hyperthermia and mitomycin C instillation. The initial cure rate after 3 months was 92% and persisted at over 50% after 2 years.
2) **Intravesical Immunotherapy:** BCG was approved by the FDA for the treatment of CIS in 1990. Immunotherapy with Bacillus Calmette Guerine (BCG) for patients with CIS has been shown to provide a favorable short-term outcome, reaching a 70% complete response.[49] Gofrit et al.[56] demonstrated that 77% of the biopsy-proven BCG responders remained progression-free 10 years later, and only 14% of them died from metastatic disease. A strong insight into the impact of BCG on CIS was achieved in two SWOG studies; the first study[57] demonstrated a 70% complete response. The median response duration was 39 months, and 64% of patients who responded to BCG remained disease-free for 5 years. The second subsequent study compared a single 6-week course of BCG with an additional 3-week course at 3 months, and the complete response rate increased by 14% with the "6+3" BCG regimen.[58,59] In patients who demonstrated complete response, maintenance BCG immunotherapy, consisting of 3 treatments at 1-week intervals for 6 month and every 6 months for 3 years, resulted in a 5-year disease-free status of more than 75%. EAU Guidelines[27] confirm the role of maintenance therapy with BCG in achieving a better cure rate in such cases. Sylvester et al.[60] demonstrated that maintenance BCG was able to prevent or delay progression to muscle-invasive tumor in patients with CIS. Davis et al.[61] demonstrated 10-year progression-free survival rates following maintenance BCG therapy of 55%, 77% and 62% for patients with CIS, high-grade Ta and T1, respectively. Van Gils-Gielen et al.[62] reported that patients with extensive CIS, defined as three or more positive biopsies or CIS associated with papillary tumors, tended to have a lower response rate, shorter time to recurrence and higher incidence of progression. In a recent study, Takynaka et al.[63] used multivariate analysis to show that the extent of CIS is the only independent factor that can predict disease progression.

   A recent investigational study showed that intravesical application of a non-viable mycobacteria (M Pheli) preparation had a promising effect for cases of documented BCG failure.[64] Watanabe et al.[65]) recommended the measurement of urinary interleukin 2 (IL 2) as a marker of BCG treatment response. Torti et al.[66] demonstrated that interferon alpha (INF-α) monotherapy is efficient for the treatment of CIS. In a more recent study, Lam et al.[67] demonstrated that combined BCG plus INF-α2B therapy may be more effective and produce a more complete response to CIS than either therapy alone.
3) **Radical Cystectomy:** EAU Guidelines recommend early cystectomy for cases that show BCG failure.[27] Delayed cystectomy in these patients may result in decreased disease-specific survival.[68] Huang et al.[69] did a retrospective study on cases that underwent radical cystectomy for CIS only of the bladder and showed excellent long-term survival outcome. The authors strongly recommended radical cystectomy for all patients who show failure of intravesical therapy. The same study also showed that patients who underwent cystectomy after failed intravesical therapy were more

likely to be understaged than those that were initially managed by cystectomy. Denzinger et al.[70] emphasized timely radical cystectomy for cases with CIS, whether alone or combined with papillary tumor, because of the deleterious effect of CIS on cancer-specific survival. Hassan et al.[71] confirmed the excellent disease-specific survival for cases with CIS treated by early cystectomy and demonstrated that these patients still exhibited a higher rate of recurrence if their disease extended into the proximal urethra.

CIS of lower ureter at the time of cystectomy

Salsona et al. found that CIS in the cystectomy specimen predicted progression to panurothelial disease (panurothelial disease is defined as the involvement of two urothelial sites, typically bladder and another site).[72]

The frequency of concomitant CIS of the upper urinary tracts at the time of cystectomy was estimated to be 8-11%.[73,74] A recent study concluded that the presence of bladder CIS can indicate concomitant ureteral CIS, and the authors recommended frozen section biopsy at the time of cystectomy in that case.[74] These researchers added that additional resection of the upper ureteral segment decreased tumor development in the upper urinary tract. Salsona et al.[72] described the elevated incidence of upper tract recurrence and increased mortality for cases with distal ureteric CIS.

Wagner et al.[75] recommended that, regardless of whether excision of the distal ureter with CIS was performed, an aggressive follow-up protocol, including ureteroscopy and selective cytology, should be performed at the time of cystectomy.

Few studies in the literature described the possibilities of recurrent CIS in the neobladder, either ileal or sigmoid, as well as ileal conduit.[76,77] Therefore, follow-up by cytology and endoscopy is highly recommended for patients after radical cystectomy.

In conclusion, CIS of the bladder can occur either de novo, secondary or concomitant to papillary tumors of the bladder. The presence of bladder CIS increases the risk of panurothelial disease involving the prostate, urethra or upper urinary tracts.

Urine cytology is the primary approach for CIS diagnosis, and it can be the only positive test for diagnosis, regardless of the inter-observer variability. Fluorescent cystoscopy should be applied whenever CIS is suspected. Wight Light cystoscopy is not sufficient for curative treatment of CIS and, when used alone, may miss multifocal CIS and increase the chance of recurrence.

Intravesical BCG remains the gold standard for the initial treatment of CIS, and a 6-week induction course alone is not adequate to establish a high cure rate for the disease; therefore, maintenance therapy with BCG should be applied for all cases.

In cases of BCG failure, there is controversy in the literature regarding the treatment choice between intravesical chemotherapy with or without hyperthermia, the addition of interferons to BCG or radical cystectomy. However; early radical cystectomy for cases that presented BCG failure showed a higher rate of success with long-term cure.

Frozen section biopsy of the distal ureter should be performed when CIS of the bladder is preoperatively diagnosed or suspected. The presence of CIS of the distal ureter necessitates its removal until a free upper margin of the ureter is reached because this approach was found to decrease the incidence of recurrent tumors of the upper urinary tracts.

Regardless of whether frozen section biopsy was performed and regardless of the condition of the distal ureter at time of cystectomy, postoperative follow-up with cytology, endoscopy of the new pouch and ureteroscopy of the ureters is recommended for the early detection of possible recurrence.

Conflict of interest

No conflict of interest was declared by the authors.

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