Bladder contracture: review for intravesical bacillus Calmette-Guerin complication

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Introduction: *We are reporting a case of bladder contracture post intravesical bacillus Calmette-Guerin (BCG) therapy; to our knowledge only two cases were reported. We present the clinical history/presentation investigation and the outcome of the treatment.*

Approximately 75%-85% of patients with bladder cancer present with disease confined to the mucosa (stage Ta-CIS) or submucosa (stage T1). The management of non-muscle invasive bladder cancer has become more complex with regard to initial investigation, treatment and follow-up. In high-grade tumors, BCG therapy has proven to be superior to intravesical chemotherapy. BCG therapy prevents, or at least delays, tumor progression.

Methods and results: *A case of high grade superficial bladder caner treated with intravesical BCG which has successfully cleared her bladder cancer nevertheless has lead to bladder contracture for which case she may need bladder reconstruction/augmentation surgery if she remained disease free added to her psychological and social effects on her life.*

Conclusion: *Although BCG is considered a very effective treatment; consensus exists that not every patient with superficial bladder cancer should be treated with BCG due to its increased risk of toxicity. Ultimately, the choice of treatment will depend upon the patient's risk of recurrence and progression.*

Assuming that maintenance therapy is necessary for optimal efficacy, the issue of BCG toxicity becomes more relevant. Due to the more pronounced side effects of BCG compared to intravesical chemotherapy, reluctance still exists about BCG use. However, with increased experience in applying BCG, the side effects now appear to be less prominent and few. Serious side effects are encountered in less than 5% of patients and this case carries one of the rarest, yet drastic, side effects of intravesical BCG.

Key Words: bladder TCC, superficial TCC, BCG treatment of bladder tumor, bladder cancer

Introduction

There are more than 10000 people diagnosed with bladder cancer each year in the United Kingdom. Bladder cancer is much more common in men than in women. Bladder cancer is the fourth commonest cancer affecting men and the tenth commonest cancer affecting women (excluding non melanoma skin cancer).

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Risk factors

Many of the etiological factors for the development of bladder tumors are known and the urologist should be aware of the types of occupational exposures that may occur to urothelial carcinogens. Aromatic amines were the first to be recognized. At-risk groups include workers in the following industries: printing, iron and aluminum processing, industrial painting, gas and tar manufacturing.[1]

Another prominent risk factor is cigarette smoking, which triples the risk of developing bladder cancer.[2] Smoking leads to higher mortality from bladder cancer during long-term follow-up, even though in a multivariate analysis the prognostic effect of smoking

was weaker than that of other factors, such as stage, grade, size and multifocality of the tumor. The profession and/or smoking habits of patients presenting with bladder cancer should be recorded.[3]

Bacillus Calmette-Guerin (BCG) has established itself as the most successful intravesical agent for the treatment of multiple forms of superficial bladder cancer. It is an attenuated mycobacterium that has been used as a vaccine for tuberculosis and that has also demonstrated antitumor activity in several different cancers. The pioneering work by Morales and colleagues in the mid-1970s bridged the beneficial properties of BCG to this accessible and immunologically responsive tumor system and thus established a standard for intravesical therapy for patients with high-risk superficial disease.

BCG remains the most effective form of intravesical therapy for prophylaxis and treatment of superficial bladder cancer. It is effective in treating carcinoma in situ as well as residual papillary disease and can be used as a prophylactic agent in recurrent superficial disease.[4]

Mechanisms of action

The exact mechanism of action of BCG is still unknown, yet it appears that BCG contacts tumor cells principally through a novel fibronectin attachment protein that is required to initiate any interaction.[5] This attachment is followed by internalization in the tumor cells. Interleukin-12, a strong polarizer of the T-helper cell (Th1) response and inducer of interferon-γ, can be detected in the urine of BCG-treated patients. This, in turn, can up-regulate the expression of intracellular adhesion molecules and the positive ratio of CD4 helper cells to CD8 cytolytic T cells.[6] Several other lines of evidence, including the expression of interleukin-2 and interferon-γ as well as the T cell populations noted at the site of BCG inflammation, suggest that a Th1 response probably mediates the therapeutic effect of BCG.[7] Multiple other cytokines can be detected in the urine and serum of BCG-treated patients, indicating that there is some degree of systemic response. There are also data to suggest that an antitumor response is associated with a delayed-type hypersensitivity reaction. The available data suggest, however, that BCG does not elicit a natural killer cell response. Work has also implicated nitric oxide synthetase induction by BCG in the bladder as an additional mechanism of its antitumor effect, because high local concentrations of nitric oxide can inhibit bladder tumor growth.[8]

Indication for BCG

Although BCG is considered a very effective treatment, consensus exists that not every patient with superficial bladder cancer should be treated with BCG due to its increased risk of toxicity. Ultimately, the choice of treatment will depend upon the patient's risk of recurrence and progression. The use of BCG will not alter the natural course of the disease in low-risk patients and may be considered over-treatment for this category.

In patients with high-risk tumors for whom a cystectomy is not carried out, no controversy exists about how to treat these patients. In multiple T1G2 tumors, Ta-T1G3 tumors with or without CIS, and CIS alone, where 15% or more of the patients will progress, the advantages of intravesical BCG are more pronounced than in intermediate-risk patients, who are at a lower risk of progression. The treatment of the remaining intermediate-risk tumors (multifocal T1G1, TaG2 and single T1G2 tumors) is more controversial. It consists of complete TUR followed by intravesical chemotherapy or intravesical BCG. The major issue in intermediate-risk tumors is to prevent recurrence and progression, of which recurrence is by far the most likely. Millan-Rodriguez et al found that, while tumor will recur in about 45% of these patients, the likelihood of progression to muscle-invasive disease is low in these patients at approximately 1.8%.[9]

Assuming that maintenance therapy is necessary for optimal efficacy, the issue of BCG toxicity becomes more relevant. Due to the more pronounced side effects of BCG compared to intravesical chemotherapy, reluctance still exists about BCG use. Early publications reporting deaths due to BCG sepsis and indicating that BCG induced cystitis occurs in up to 90% of patients have strongly compromised the use of BCG.[10]

Side effects of BCG therapy

BCG is generally well tolerated with only moderate side effects, yet the potential for serious illness and death exists. Most patients experience dysuria and urinary urgency and frequency that last for several days and worsen during the course of therapy. These side effects may be treated symptomatically with mild anticholinergics, acetaminophen, or phenazopyridine. Hematuria may also be present in approximately 30% of patients. Persistent microscopic hematuria is a relative contraindication for BCG delivery.

Granulomatous prostatitis can be an asymptomatic finding in 20% to 30% of patients and may cause

elevated serum prostate-specific antigen. This condition is symptomatic in approximately 1% of cases. Testicular involvement is less common but may progress to orchiectomy if untreated. Bladder contracture is seen in less than 0.5% of patients treated with BCG.

Low-grade fever or slight malaise may occur in a large proportion of patients. If fever higher than 38.5°C persists for longer than 24 hours and does not resolve with antipyretic therapy or if fever higher than 39.5°C is encountered, treatment with isoniazid (300 mg daily for 3 months) is necessary. Systemic BCGosis is generally manifested as pulmonary or hepatic disease and is a serious condition. This form of disease warrants a combination of isoniazid-rifampin for 6 months with addition of ethambutol in acutely ill patients. Pyridoxine is added to any long courses of isoniazid treatment. BCG sepsis is a rare (0% to 4%) yet life-threatening condition that should be treated with standard life support methods as well as triple drug therapy. In any case of local or systemic illness with BCG, it is also important to evaluate common urinary pathogens as a cause and treat appropriately.

Treatment of prostate transitional cell carcinoma with TUR is appropriate. Carcinoma of the mucosa or the superficial ducts of the prostate can be adequately treated by BCG. A limited TUR of the gland can be effective in decreasing tumor burden and facilitating exposure of the prostate surface to BCG administration. Tumor-free rates of 50% can be attained in this manner.[11]

Case study

A 50-year-old woman presented to the urology clinic in 2002 with few episodes of frank hematuria of few weeks duration. Clinical examination was unremarkable.

Flexible cystoscopy showed a large papillary tumor close to the bladder neck. An IVU showed normal kidneys. The patient was on the waiting list for TURBT.

The patient underwent TURBT and had intravesical mitomycin (40 mg) in the immediate postoperative period. Histology suggested G3 PT1 transitional cell carcinoma of the bladder with no muscle invasion. A repeat resection 4 weeks later also confirmed superficial nature of the disease. Staging investigation revealed no extravesical disease.

After discussion in multidisciplinary team meeting a six week course of intravesical BCG (ImmuCyst® 81 mg) was commenced 4 weeks after TURBT. The patient tolerated the treatment quite well. Check cystoscopy was done 4 weeks after the completion of the course. Bladder biopsies revealed no evidence of recurrent disease.

A maintenance course involving one weekly instillation of BCG for 3 weeks, every 6 months for 3 years was commenced. Regular cystoscopies were done to ensure normal bladder. After four cycles, she progressively developed bladder pain and intense storage symptoms of nocturia, frequency and urgency.

An urgent cystoscopy was done and it revealed a small capacity bladder of 150 ml and multiple bladder biopsies were done. The histology showed no evidence of recurrent disease but features consistent with severe follicular cystitis.

A repeat CT scan of her pelvis revealed normal study. Further BCG treatment was stopped. Regular check cystoscopies were done. Bladder capacity continued to be 150 ml. She continued to have with considerable symptoms refractory to anticholinergics, intravesical anti inflammatory instillations, and Elmiron.

Repeated bladder biopsies over the last 3 years confirmed that there was no evidence of recurrent G3 disease but continued to show features of chronic inflammation. Tuberculous bladder was also entertained but the bladder biopsy failed to culture any acidfast organisim. Urine culture was negative for tuberculous bacilli and bladder biopsy was not suggestive of tuberculous bladder.

The BCG has cleared her cancer but she developed bladder contracture secondary to BCG. The dose of mitomycin and/or the number of TURBTs were very little to encounter for this problem. This is one of the rare cases that ended to this even rarer complication and the plan of management was discussed with specialist in the region for surgical options. Cystectomy and / or bladder reconstruction may be the only option if she continues to be disease free and her symptoms worsened.

Discussion

Litreature review has found only two articles of similar complication. In one of them a 35-year-old man had undergone retroperitoneoscopic radical nephrouretectomy for (pTisNxM0). He later developed carcinoma in situ (CIS) of the bladder, and underwent intravesical instillation of 80 mg of BCG once a week for 6 weeks in January 2004. After the treatment, irritative symptoms (frequency and dysuria) developed, and he was diagnosed with bladder contracture. Conventional treatment with anti-cholinergics, analgesics, anti-tuberculous drugs, and steroids was ineffective, but hydrodistention improved the subjective symptoms. Hydrodistention seems to be useful for bladder contracture following intravesical BCG immunotherapy.[12]

The second one is a paper published in 1993 were intravesical BCG immunotherapy has lead to bladder contracture. Two cases of persistent small-capacity bladders occurring more than 1 year after intravesical BCG therapy.[13]

The effect of the immediate instillation of chemotherapy occurs during the first and second year. It has been calculated from the data of five randomized trials that the reduction of recurrence lasts for a period of approximately 500 days. The choice between chemotherapy or immunotherapy largely depends on the risk that needs to be reduced: recurrence or progression. Adjuvant chemotherapy bladder instillations are effective in preventing recurrence in low-grade tumors. In high-grade tumors, BCG therapy has proven to be superior to intravesical chemotherapy. Two meta-analyses demonstrated that BCG therapy prevents, or at least delays, tumor progression.[14]

Patients with local BCG side effects had a significantly longer time to first recurrence, suggesting that side effects are related to efficacy. However patients with a better outcome remain to receive more BCG, thus increasing their risk to develop side effects.

Neither the delay nor stop of BCG due to local toxicity and/or systemic toxicity prior to 6 months was related to the time to subsequent recurrence. Likewise there was no relationship to the particular type of local (BCG cystitis, frequency, hematuria) or systemic (general malaise, fever) toxicity or their degree. Thus although the reporting of side effects and the decision to modify the treatment are, at least to some extent, subjective in nature and will vary from one institution to another.

BCG is generally well tolerated, but severe adverse reactions can occur. Symptoms of cystitis occur in up to 90% of treated patients. Dysuria, frequency, low-grade fever, and malaise usually develop after the third instillation. These responses are usually self-limited, lasting about 24 hours. Such symptoms are best viewed as anticipated responses of the immune stimulation, rather than as adverse reactions. Most patients respond to symptomatic treatment with anticholinergics, pyridium, or nonsteroidal anti-inflammatory medications.

Significant reactions to intravesical BCG occur in only 5% of patients. Fever greater than 39.4°C is the most common reaction, occurring in 3% of all patients. The febrile period is usually limited to 48 hours or less. The main concern with fever is the inability to distinguish an uncomplicated febrile episode from the onset of systemic BCG infection or hypersensitivity sepsis. Patients in whom a high fever develops should therefore be hospitalized for observation and treated daily with isoniazid 300 mg and rifampicin 600 mg. BCG sepsis has been observed in approximately 0.4% of patients treated with intravesical BCG, and to date, 10 deaths have been attributed to intravesical BCG.[15]

Other adverse reactions of intravesical BCG therapy include hepatitis or pneumonitis, each in 0.7% of patients, arthritis and migratory arthralgia in 0.5%, skin rash in 0.3%, epididymitis/orchitis in 0.4%, ureteral obstruction in 0.3%, and bladder contracture in 0.5%.[16]

It is very evident from the above that this is a very rare case and very few are reported over a long period and despite the rarity of the condition it has a sever implication; on one aspect is the patient's life, her wellbeing and the management plan as it may need a properly planned surgery to rectify the reduced bladder capacity if she remained disease free and on the other aspect is the economical burden on the health authority. □

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