Reactive Arthritis After Intravesical Bacillus Calmette-Guérin Therapy

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Abstract: Reactive arthritis (ReA) is a sterile arthritis that occurs in genetically predisposed individuals secondary to an extra-articular infection, usually of the gastrointestinal or genitourinary tract. Sterile arthritis associated with instillation of intravesical bacillus Calmette-Guérin (iBCG) therapy used for bladder cancer can also be included under ReA based on the pathogenic mechanism. Similar to spondyloarthritis, HLA-B27 positivity is a known contributor to the genetic susceptibility underlying iBCG-associated ReA. Other genetic factors, such as HLA-B39 and HLA-B51, especially in Japanese patients, can also be involved in the pathophysiology of iBCG-associated ReA. The frequencies of ReA- and ReA-related symptoms are slightly different between Japanese and Western studies. Proper understanding of possible complications, their epidemiology and pathogenesis, and their management is important for the rheumatologist when noting symptomatic patients using iBCG. Herein, we will review the most current information on ReA after iBCG therapy.

Key Words: reactive arthritis, intravesical, bacillus Calmette-Guérin, BCG, bladder cancer

INSTILLATION OF INTRAVESICAL BACILLUS CALMETTE-GUÉRIN FOR BLADDER CANCER

Instillation of intravesical bacillus Calmette-Guérin (iBCG), also known as *Mycobacterium bovis*, is a long-standing treatment for bladder cancer. BCG was originally developed as a vaccine against tuberculosis. In 1976, Morales et al[1] were the first to report the clinical efficacy of iBCG against bladder cancer. Since then, comparative studies have proven BCG to be consistently superior to other anticancer drugs, and iBCG immunotherapy has been regarded as the criterion standard adjuvant therapy for high-risk

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non–muscle invasive bladder cancer and carcinoma in situ (CIS) after complete transurethral resection of bladder tumors.[2,3] It is currently estimated that there are 75,000 and 20,000 new cases of bladder cancer (including CIS) per year in the United States and Japan, respectively,[4,5] with higher incidences of bladder cancer observed in aging societies. Therefore, for many clinicians, including rheumatologists, obtaining an understanding of iBCG is imperative.

For iBCG therapy, a BCG solution mixed with normal saline is delivered directly into the bladder through a catheter for approximately 2 hours. The iBCG treatment includes both an induction and a maintenance phase. Induction therapy by iBCG involves weekly instillations of iBCG for 6 to 8 weeks. Moreover, maintenance therapy by iBCG involves 3 once-weekly instillations at 3, 6, 12, 18, 24, and 36 months.[1,2,6]

IBCG-INDUCED IMMUNITY/IBCG MECHANISMS OF ACTION IN BLADDER TUMORS

According to recent evidence, iBCG-induced specific tumor immunity involves several critical steps, culminating in the simultaneous eradication of both the pathogen and tumor cells. First, attachment—BCG attaches to fibronectin on urothelial cells, mostly urothelial carcinoma cells (UCCs), via a fibronectin attachment protein. Likewise, bladder-resident antigen-presenting cells (APCs), such as macrophages (MQs) and dendritic cells (DCs), can recognize BCG pathogen-associated molecular patterns through various pattern recognition receptors such as toll-like receptors (TLR2 and TLR4), complement receptors, and DC-specific ICAM-3–grabbing nonintegrin. Second, internalization and processing—BCG is internalized after attachment, and its antigens (Ags) are further processed by APCs, leading to the activation of both UCCs and APCs and the production of a variety of proinflammatory cytokines and chemokines (tumor necrosis factor α [TNF-α], granulocyte-macrophage colony-stimulating factor [GM-CSF], interleukin [IL]-1β, IL-6, IL-8, IL-12, IL-15, and so forth). In this step, immature DCs can migrate to adjacent lymph nodes, where they present Ags to naive T cells upon maturation, resulting in the potent induction of effector T-cell responses ($T_H1/17$ and CTL). In UCCs, BCG is also demonstrated to directly exert tumoricidal effects by enhancing Ag presentation (upregulation of human leukocyte antigen [HLA] Ags), cell cycle arrest (upregulation of p21), and expression of cytokines and chemokines (IL-1β, IL-6, IL-8, TNF-α, and GM-CSF). Third, recruitment of adaptive and innate immune cells—chemokines generated as the result of the previous stage attract various leukocytes (neutrophils, monocytes/MQs, DCs, lymphocytes, and natural killer cells) to the bladder wall. Fourth, amplification of immune cell activation and formation of granulomas—recruited cells further amplify immune responses by generating a variety of additional proinflammatory cytokines and chemokines, ultimately inducing the formation of BCG granulomas. Indeed, it has been reported that several cytokines, chemokines, and leukocytes can be detected in voided urine after instillation of iBCG, including neutrophils, T cells, MQs, GM-CSF,

monocyte chemoattractant protein 1, C-C motif chemokine ligand 2, TNF-α, interferon γ (IFN-γ), IL-1β, IL-2, IL-6, IL-10, IL-12 IL-15, IL-18, and so on. Fundamentally, attracted leukocytes have been illustrated to eradicate cancer cells via several mechanisms, such as producing and expressing reactive oxygen intermediates, TNF-related apoptosis-inducing ligand, cytolytic enzymes, and TNF-α. Thus, the development of a T_H1 microenvironment (IFN-γ, IL-2, and IL-12) is associated with successful BCG immunotherapy, whereas a suppressive microenvironment (T_H2; myeloid-derived suppressor cells, innate lymphoid cell 2, and IL-10) is correlated with failure of BCG.[4,7–12]

MAIN ADVERSE EFFECTS AND COMPLICATIONS OF IBCG THERAPY

Adverse reactions and complications of iBCG therapy can be grouped based on their localization and severity.[13,14]

Adverse reactions and complications categorized by localization consist of local/genitourinary and systemic complications. These complications include cystitis (27%–95%), bladder contracture (<1%), bladder ulceration (1.5%), penile nodules/papules/plaques/ulcers (5.9%), tuberculous epididymo-orchitis (0.4%), symptomatic prostitis (10%), ureteral obstruction (0.3%), and kidney infections (0.3%–3.5%). On the other hand, systemic complications include fever (1.4%–16.4%), mycotic aneurysms (0.7%–4.6%), miliary pulmonary tuberculosis (0.4%), granulomatous hepatitis (0.7%–5.7%), reactive arthritis (ReA; 0.5%–5.7%), tuberculous spondylitis (3.5%), and disseminated BCG infection/BCG sepsis (0.4%).[13–19]

Adverse reactions and complications are categorized by severity (grades 1, 2, and 3) along with the time from the last instilled dose, as follows: grade 1, minor and moderate symptoms, including irritable voiding symptoms, low-grade fever, and gross hematuria within the first 48 hours after instillation; grade 2, severe symptoms, including high-grade fever, ReA, miliary pulmonary tuberculosis, hepatitis, and so forth, from 48 hours after instillation; and grade 3, serious complications encompassing a broad sepctrum of solid organ systems within the body, including hemodynamic instability due to BCG sepsis and severe allergic reactions.[13,14]

Especially in ReA, clinical symptoms occur between 1 and 3 weeks after the last iBCG therapy before the onset of ReA and include osteoarticular (polyarthritis/oligoarthritis/monoarthritis), urinary (urethritis), ocular (conjunctivitis/uveitis), and systemic (fever) manifestations (Fig. 1).[19–21]

As an osteoarticular manifestation, arthritis can occur in the hands, knees, ankles, and other joints, especially in the lower extremities, with polyarthritis occurring in 50%, oligoarthritis in 40%, and monoarthritis in 10% of cases.[19–21] Although both polyarthritis and oligoarthritis can be either symmetric or asymmetric, an asymmetric distribution is more prevalent in oligoarthritis (Fig. 2). Enthesitis and dactylitis can also be present.[19–21]

Urethritis is a urinary symptom that preceeds arthritis and is characterized by painful urination, pollakisuria, hematuria, bladder irritation, and pyuria.[19,20]

The observations of severe redness, pain, and photophobia indicate conjunctivitis/uveitis. Conjunctivitis is the most frequent eye symptom observed in the patints (approximately 40% of the cases), whereas uveitis occurs in approximately 8% of the patients. In approximately 30% of patients, conjunctivitis preceeds arthritis, and it follows arthritis in approximately 10%.[19,20,22,23] Table presents a comparison of the frequencies of main iBCG complications, especially ReA-related symptoms, between Japanese and Western reports.[13,14,18,22–24]

EPIDEMIOLOGY OF REA AFTER IBCG THERAPY

Reactive arthritis is a nonpyogenic arthritis that primarily develops within 1 month after intestinal infection with *Shigella*, *Salmonella*, *Campylobacter*, and *Yersinia*, or urinary tract infection
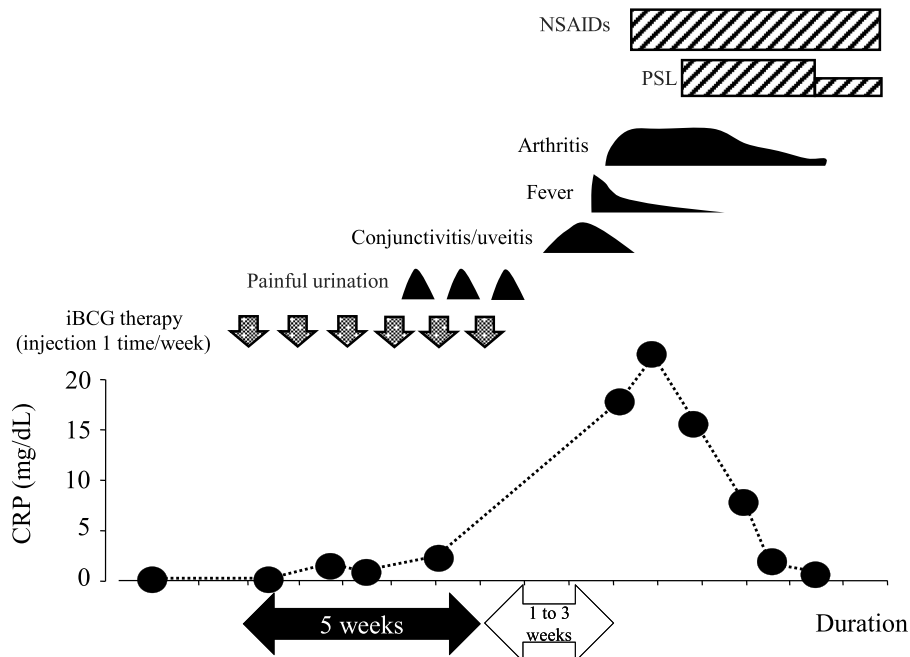
FIGURE 1. Clinical course of ReA after iBCG. The onset is indicated by painful urination occurring after 4 to 6 sessions of iBCG therapy, and conjunctivitis/uveitis, fever, and arthritis develop from 1 to 3 weeks after the last iBCG. Some patients might require several treatments, including NSAIDs and PSL, for severe or prolonged symptoms, and the treatments can shorten the natural duration of the disease. CRP indicates C-reactive protein; PSL, prednisolone.
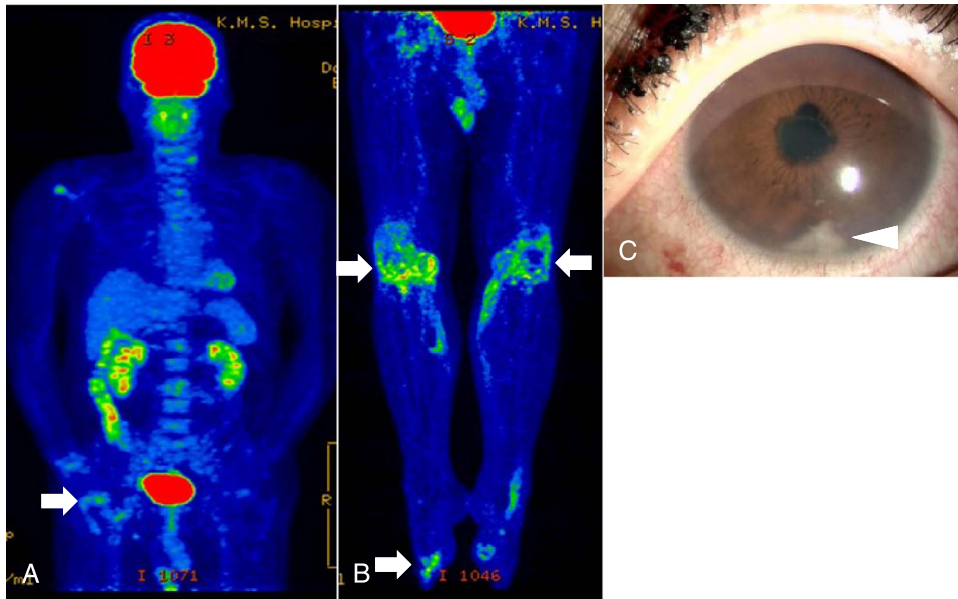
FIGURE 2. Clinical and imaging findings of ReA after iBCG therapy. A and B, Fluorodeoxyglucose positron emission tomography. Images show the asymmetric distribution of arthritis, especially in the lower extremities with high FDG uptake (white arrows). C, Uveitis with hypopyon (white arrowhead) in a patient with ReA after iBCG therapy.

with *Chlamydia*.[25] In addition, ReA is known to occur as an adverse reaction or complication of iBCG therapy. In Western countries, the incidence of ReA after iBCG therapy ranges from approximately 0.5% to 5.7%.[20,22,23] Meanwhile, our survey suggests that the incidence ReA after iBCG therapy is approximately 2% in Japan[18] (Table). Of course, in our Japanese survey, long-term mycobacterial cultures in synovial fluid and blood were performed in all patients with ReA, and the results showed no growth or negative findings, suggesting the exclusion of disseminated BCG infection. Because of the high rate of tuberculosis infection in Japan, BCG vaccination before the age of 1 year is now established, and its administration is enforced as a law in Japan. Although the reasons for the higher incidence of ReA after iBCG therapy in Japan as compared with that in Western countries remain unknown, a history of BCG vaccination or genetic factors including HLA-B39 and HLA-B51 peculiar to the Japanese population might have an influence.

The ratio of males to females developing ReA after iBCG therapy is greater than 3:1, indicating that the condition is more common in males. The development of ReA in elderly patients is almost always attributed to the fact that all patients with bladder cancer treated with iBCG are older than 70 years. The onset of ReA generally occurs after approximately 4 to 6 iBCG therapy sessions, with approximately 90% of patients experiencing onset 3 weeks or less after their last iBCG treatment. However, because some patients can develop the disease as early as the second instillation, careful interview and examination at outpatient clinics are required. To limit the occurrence of adverse events, several recent attempts have been performed as follows: (1) the dose of BCG administered in each intravesical therapy has been reduced while keeping the number of doses unchanged (eg, the dose for Immunobladder has been reduced from 80 to 40 mg); (2) in the priming-boosting strategy (ie, following the priming step), physicians perform a purified protein derivative tuberculin test, and only if the results are indicative of a strong immune response, iBCG can be instilled; and (3) the measurement of voided urine cytokines after the first instillation might assist in earlier detection. Although the incidence of ReA with these reduced doses of instillation of iBCG is unclear, it is possible that ReA can still occur.[13,14,26] Thus, continued caution is needed.[18–21]

TABLE. Comparison of Frequencies of Main iBCG Complications, Especially ReA-Related Symptoms, Between Japanese and Western Reports

Complication	Japanese Reports[a] (n [%] of Total 555 Patients)	European Reports[b] (n [%] of Total 282 Patients)	North American Reports[c] (n [%] of Total 1278 Patients)
Fever	91 (16.4%)	4 (1.4%)	50 (3.9%)
Arthritis (reactive arthritis)	11 (2.0%)	16 (5.7%)	6 (0.5%)
Conjunctivitis	33 (5.9%)	NA	NA
Uveitis	4 (0.7%)	7 (2.4%)	NA

[a]Data modified from Taniguchi et al. *Joint Bone Spine* 2017;84:637–638.
[b]Data modified from Pérez-Jacoiste Asín et al. *Medicine (Baltimore)* 2014;93:236–254.
[c]Data modified from Lamm et al. *J Urol* 1986;135:272–274 and Koya et al. *J Urol* 2006;175:2004–2010.
NA, not available.

ETIOLOGY AND PATHOGENESIS OF REA AFTER IBCG THERAPY

After local infection with certain bacteria, the bacteria likely persist at the primary infection sites or their adjacent lymph nodes (incomplete eradication of the infection). Thereafter, the bacteria or their Ags can be transported from these primary sites into the synovium, either directly via the blood or indirectly by phagocytes (monocytes), resulting in an altered local immune response in genetically susceptible individuals. Thus, ReA development depends on a combination of contributors: (1) microbial agents (intracellular Gram-negative bacteria), (2) genetic factors (HLA-B27 positivity and single-nucleotide polymorphisms in TLR2), and (3) an aberrant synovial immune response (unbalanced production of TNF-α [decreased in acute ReA and elevated in chronic ReA], IFN-γ [decreased in acute ReA], IL-6 [elevated in ReA], IL-10 [increased in ReA], IL-17 [elevated in ReA]). The prevalence of positive HLA-B27, an allele of the polymorphic major histocompatibility complex I molecules, has been illustrated to range from 50% to 80% in ReA cases. The arthritogenic peptide hypothesis is among the potential mechanisms linking HLA-B27 to ReA. This hypothesis explains that HLA-B27+ APCs initially present a bacterial-derived peptide to CD8+ T cells in primary infection sites. The activated CD8+ T cells then translocate to joints, where they respond to self-peptides presented by HLA-B27 on synovium cells due to molecular mimicry. Other hypotheses include the misfolding and heavy-chain homodimer formation hypothesis.[27–29]

With regard to the immunopathogenesis of ReA after iBCG therapy, it has been shown that iBCG therapy can provoke a systemic hypersensitivity reaction (both CD4+ and CD8+ T cells) in addition to the previously discussed local immunity. Therefore, activated and memory immune cells may translocate to joints, resulting in the development of arthritis (Fig. 3).[9,30,31] The prevalence of ReA after iBCG therapy in patients who are HLA-B27 positive has been reported to be 50.9% to 53% in Western countries.[20] In line with these observations, a BCG-induced cytotoxic immune response has been suggested to be triggered in the synovium via cross-reactivity with an endogenous heat shock protein presented by HLA-B27.[32] However, prior studies have reported that the prevalence of HLA-B27 positivity is lower in Japan.[18] Furthermore, some Japanese patients have HLA-B51, whereas others have HLA-B39.[18,19,33,34] Therefore, other genetic factors might also be involved in the pathophysiology of iBCG-associated ReA.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

As with classical ReA, the diagnosis of ReA after iBCG therapy has been obtained in the clinic based on the pattern of findings and exclusion of and differentiation from other diseases. There is no single definitive diagnostic test or established diagnostic criteria for ReA resulting from iBCG therapy. The most important consideration is that ReA is an adverse reaction to iBCG therapy; thus, it is critical to inquire closely about a history of iBCG therapy after conducting a complete evaluation of symptoms. Similar to classical ReA, a differential diagnosis of acute monoarthritis, oligoarthritis, or polyarthritis is needed from a wide range of disorders, including rheumatoid arthritis, septic arthritis, other infection-related arthritis, and crystal-induced arthritis, among others. A clinical diagnosis requires a comprehensive evaluation of clinical characteristics sufficient to allow a conclusive differentiation from and exclusion of other disorders.

Clinical laboratory findings have demonstrated the following characteristics. In almost all patients with ReA after iBCG therapy, the acute phase is characterized by an increase in serum inflammatory marker (C-reactive protein level and erythrocyte sedimentation rate). Rheumatoid factor, anticyclic citrullinated peptide antibody, and antinuclear antibody are negative in all cases, suggesting exclusion of rheumatoid arthritis and other connective tissue diseases. Reactive arthritis after iBCG therapy is less strongly associated with HLA-B27 than classical ReA is.[18,20] Not only HLA-B27 but also HLA-B35, HLA-B39, and HLA-B51 can be involved in the pathophysiology of iBCG-associated ReA.[18–20] Although the presence of bacterial DNA in the joint fluid of patients with ReA after iBCG therapy has been reported,[30] synovial
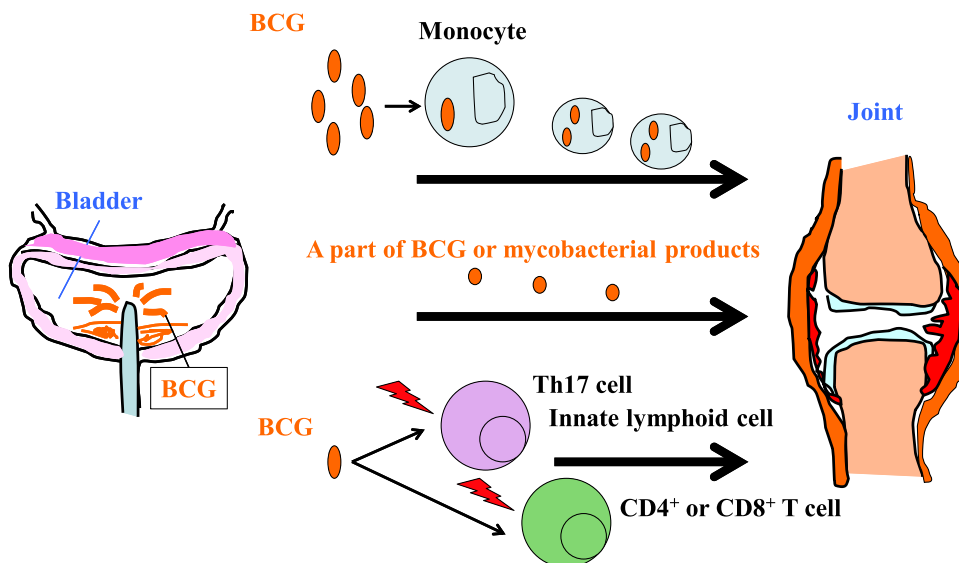
FIGURE 3. Hypothesized pathogenesis of ReA after iBCG therapy. The bladder is a major site of bacterial invasion, which leads to the activation of local T_H17 cells and innate immune cells, including natural killer cells, in ReA after administration of iBCG therapy for bladder cancer. These activated innate immune cells may subsequently translocate to joints, resulting in the development of arthritis. Moreover, similar to classic ReA, microbes can also reach the synovial cavity, either directly through the blood or by transport within phagocytes (monocytes) in ReA after iBCG therapy.

fluid analysis has basically shown that bacterial and mycobacterial cultures were negative, indicating no presence of viable mycobacterium.[19,20,30] Blood cultures were also negative in all cases. Therefore, the results of synovial fluid and blood culture can exclude disseminated BCG infection. Moreover, analysis of synovial fluid demonstrated no urate and calcium pyrophosphate crystals, suggesting the exclusion of crystal-induced arthritis.

TREATMENT

The first treatment action should be the discontinuation of iBCG therapy until the complete resolution of symptoms, and a benefit-risk assessment must be conducted before resuming iBCG treatment. Similar to other forms of ReA, nonsteroidal anti-inflammatory drugs (NSAIDs) are considered first-line treatment. For conjunctivitis/uveitis, corticosteroid eye drops are initially recommended. However, refractory cases and oral steroids (second-line agents) are an option. Intra-articular injections of corticosteroids can also be considered for reducing the symptoms of large joints. Second-line agents include both systemic corticosteroids and disease-modifying antirheumatic drugs (DMARDs). For patients with serious symptoms or inadequate response to NSAIDs, low to moderate doses of systemic corticosteroids (oral prednisolone 10 to 20 mg daily) are administered. Alternatively, for severe cases refractory to NSAIDs or steroids or that may become chronic, DMARDs (sulfasalazine and methotrexate) may be used.[20,21,35] Biological agents can be considered as the third-line treatment for patients' refractory to first- and second-line treatment, but these agents should be used with caution as the last choice to wean prednisolone dose. For instance, tocilizumab, an anti–IL-6 receptor monoclonal antibody, has shown promise in treating refractory ReA, but further investigation is warranted to ascertain its efficacy.[36] Antitubercular drugs (isoniazid and rifampicin) have also been used to treat these patients, most often with corticosteroids and NSAIDs. Notably, remission is typically induced after the patient receives either monotherapy with NSAIDs, corticosteroids, and antitubercular agents or different combined regimens of NSAIDs, corticosteroids, DMARDs, and antitubercular agents. However, there have been reports of cases progressing to chronic persistent arthritis. Thus, treatment should be continued until complete recovery, which usually happens within 3 months.[19–21,34,35]

CONCLUSIONS

Sterile arthritis associated with iBCG immunotherapy is regarded as the criterion standard adjuvant therapy for high-risk non–muscle invasive bladder cancer and CIS after complete transurethral resection of bladder tumor and could be included in the entity of ReA. Genetic fators including not only HLA-B27 but also HLA-B39 and HLA-B51 might be pivotal contributors to the genetic susceptibility underlying iBCG-associated ReA. Thus, the frequencies of ReA- and ReA-related symptoms might be slightly different between Japanese and Western reports. The incidence of bladder cancer increases depending on the presence of an aging society, and it is important for the rheumatologist to have a proper understanding of the possible complications, their epidemiology and pathogenesis, and their management when focusing symptomatic patients using iBCG.

KEY POINTS

- Sterile arthritis is an adverse effect of iBCG therapy for bladder cancer and can be classified as ReA.
- Similar to the pharynx, tonsil, and intestine, the bladder is a key site of bacterial invasion, which can lead to the activation of local T_H17 cells and innate immune cells, including natural killer cells in ReA after iBCG therapy for bladder cancer.
- However, a number of issues related to the pathogenesis of the disease, including its association with HLA-B27, and therapeutic strategies require further study.

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