CASE REPORT

New-onset guttate psoriasis following intravesical immunotherapy of Bacillus Calmette–Guerin

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ABSTRACT
Intravesical Bacillus Calmette–Guerin (BCG) is usually a well-tolerated treatment for urothelial carcinoma of the bladder. A 60-year-old male endured multiple erythematous white-scaled maculopapules over his trunk, back, and four extremities after 2 months of the 6-weekly intravesical instillation of BCG. Skin biopsy revealed parakeratotic hyperkeratosis, intracorneal neutrophilic Munro’s abscess, and acanthosis. Guttate psoriasis was diagnosed, and he was treated successfully with topical steroid and narrow band UV-B phototherapy. We present the first Asian case of guttate psoriasis associated with intravesical BCG immunotherapy and review the literatures.

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Introduction
Several cutaneous complications have been reported with the use of intravesical Bacillus Calmette–Guerin (BCG) immunotherapy, the mainstay treatment for superficial bladder cancer. These complications have included granulomatous lesions of the penis, painful ulcers and papules, and inguinal lymphadenopathy. Here, we describe a case with new-onset guttate psoriasis after the completion of one course of intravesical BCG immunotherapy.

Case report
After diagnosis with high-grade urothelial carcinoma of the bladder, clinical stage T1N0M0, a 60-year-old male underwent intravesical BCG immunotherapy in the form of 6-weekly intravesical instillations of BCG. Two months after the sixth BCG instillation, multiple skin lesions appeared on the patient’s trunk, back, and four extremities. The patient had no history of psoriasis or other systemic diseases, and no signs of acute upper respiratory tract infection had been noted before the onset of the skin lesions. Furthermore, no family history of psoriasis was traced.

Physical examination revealed numerous scattered asymptomatic erythematosus white-scaled papules and plaques involving the trunk, back, and four extremities as well as Auspitz’s sign, but no pitted nails or dermatological complications of the scalp, face, or palmoplantar regions (Figure 1A). The results of tissue biopsy from the medial aspect of the right forearm revealed the presence of parakeratotic hyperkeratosis, acanthosis (Figure 2A), and intracorneal neutrophilic Munro’s abscess (Figure 2B). Observation of immunohistochemical staining with activated phospho-Stat-3 (Tyr705; 1:1000) and psoriasin (S100A7; 1:750) revealed the concentration of the former in the nuclei of the keratinocytes (Figure 3A) and of the latter in the epidermis of the lesions (Figure 3B). Based on these clinical and pathological findings, the patient was diagnosed with guttate psoriasis.

The patient was treated with 18 applications of systemic narrow-band UV-B phototherapy (300–1200 mJ) and twice-daily application of 0.1% diflucortolone valerate cream on the lesions. This treatment, which relieved his symptoms, resulted in the development of Woronoff’s rings in the normal skin adjacent to the psoriatic macules (Figure 1B). Three weeks after beginning dermatological therapy, the patient resumed BCG instillation immunotherapy to treat his bladder cancer. As anticipated, the extent of his guttate psoriasis worsened with the resumption of BCG instillation immunotherapy.

Discussion
Vaccination with BCG, a live attenuated Mycobacterium bovis vaccine used to stimulate the immune system and prevent severe forms of infection caused by mycobacterium tuberculosis, is practiced on a national scale in Taiwan. However, several dermatological
complications have been reported with BCG vaccination, with the severity of the complications depending on the immunity of the host. Skin complications that have been reported in immuno-competent hosts include juvenile sarcoidosis over the dorsum of the hands and feet,1 keloid and delayed tuberculoid granuloma formation on the BCG vaccination site,2 and granulomatous inflammation of vaccination site in patients with Kawasaki’s disease.3 In 1955, Raaschou-Nielsen4 reported the first case of psoriasis following BCG vaccination that appears in the literature.

In 2004, Koca et al5 reported the successful treatment of a case in the form of guttate psoriasis-like lesions on a 7-year-old boy 1 week after BCG vaccination with 3 weeks of topical corticosteroid therapy.

In addition to serving a means of vaccination, intravesical BCG immunotherapy is regarded as a standard and well-tolerated means of treating superficial bladder cancer. The mechanism underlying the therapeutic effect of BCG instillation is induction of inflammation and stimulation of helper and killer T lymphocytes,

Figure 1 (A) Multiple erythematous white-scaled maculopapules involving the trunk, back, and four extremities. (B) After narrow band UV-B and topical steroid treatment, Woronoff’s rings developed in the normal skin adjacent to psoriatic macules.

Figure 2 Histological features of the lesion. (A) The macule located on the medial side of forearm reveals hyperkeratotic acanthosis with a dermal cellular infiltration [hematoxylin and eosin (H&E), 40×]. (B) There are multiple intracorneal neutrophilic Munro’s abscess (H&E, 400×).

Figure 3 Immunohistochemical staining showing (A) Phospho-Stat-3 [1:1000; Phospho-Stat-3 (Tyr705) antibody; Cell Signaling Technology Inc., Beverly, MA, USA] is expressed in the nuclei of the keratiocytes (400×). (B) Psoriasin (S100A7; 1:750; Abcam, Cambridge, MA, USA) is expressed in the whole layer of the epidermis (400×).
which is hypothesized to be responsible for the destruction of tumor cells. The complications of BCG immunotherapy range from irritative lower urinary tract symptoms to sepsis. The side effects include granulomatous prostatitis, epididymo-orchitis, hepatitis, and pneumonitis. Several cutaneous side effects have also been reported, with two case reports describing the development of granulomatous lesions of the penis accompanied with penile swelling and edema, painful ulcers and papules, and inguinal lymphadenopathy after six instillations of BCG treatment. The mycobacterial stain and cultures of both cases were negative, but both were treated successfully with antitubercular regimens.

The other rare cutaneous complication that has been reported is psoriasis, of which only two cases have been described in the literature (Table 1). In 1995, Queiro et al first reported the exacerbation of psoriatic polyarthropathy with dactylitis in a 52-year-old man with psoriasis following BCG immunotherapy. After suspension of BCG treatment, the patient was successfully treated with non-steroidal anti-inflammatory drugs and steroid infiltrations. In 2008, Dudelzak et al reported the first case of new-onset psoriasis and psoriatic arthritis after instillation of BCG. With treatment of etanercept and topical steroids, the patient’s symptoms significantly improved. In the case of new-onset guttate psoriasis following intravesical BCG immunotherapy reported here, the patient was successfully treated with topical steroids and narrow-band UV-B phototherapy but experienced relapse after resumption of BCG instillation.

The relationship between guttate psoriasis and intravesical BCG instillation remains uncertain, with the activated immune system hypothesized to play an important role in psoriasis pathogenesis. The mechanism by which intravesical BCG treats bladder cancer is a complex process that is also not completely understood. Based on the knowledge that BCG particles are internalized and processed by antigen-presenting cells and tumor cells, it is hypothesized that BCG antigens are present on the cell surface where, via major histocompatibility complex molecules, they activate T lymphocytes. Such activation may induce inflammation, which in turn induces the production of several cytokines, including interferon-gamma, tumor necrosis factor-beta, and interleukin (IL)-1, 2, 5, 6, 8, 10, 12, and 18. IL-6 production and BCG internalization relate to the differentiation of the tumor cells. In contrast to the well-differentiated transitional cell carcinoma (TCC) cells, the poorly differentiated cell lines have been found to allow them to internalize BCG and up-regulate IL-6 synthesis. This finding correlates with the clinical observation of a lower recurrence rate of high-grade TCC with BCG instillation compared to low-grade TCC.

IL-6 has been found to induce not only differentiation of Th17 cells but also production of IL-22 from naïve T cells. In addition to the finding that IL-22 induces the proliferation of keratinocytes and activates Stat-3 with nuclear localization and production of psoriasin (S100A7), both Th17 and IL-22 play important roles in the pathogenesis of psoriasis. In the present case, activated phospho-Stat-3 was found in the nuclei of keratinocytes in the skin lesion (Figure 3A), and psoriasin was strongly stained in the entire epidermis of lesional skin (Figure 3B). Both findings may suggest an activation of IL-22 in the psoriatic plaque of our patient.

In conclusion, we report a case of guttate psoriasis after the intravesical BCG instillation for the treatment of urothelial carcinoma of the bladder. He was treated successfully with narrow-band UV-B phototherapy and topical corticosteroids. Nowadays, use of intravesical BCG immunotherapy for the superficial bladder cancer is quite common. Dermatologists should be aware of this potential cutaneous complication of BCG therapy.

References


Table 1 Clinical features of cases with psoriasis associated with intravesical Bacillus Calmette-Guerin (BCG) published in the literature.

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex/age and race</th>
<th>Location/morphology</th>
<th>Bladder cancer (grading)</th>
<th>Past history of psoriasis</th>
<th>Additional findings</th>
<th>Treatment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M/52 NA</td>
<td>Plaques of psoriasis on the elbows</td>
<td>Grade III</td>
<td>Yes</td>
<td>Fever, oral ulcer, synovitis in both wrists, MCP joints and right knee, dactylitis in the second toe of the left foot, and the forth toe of the right foot</td>
<td>NSAIDs and steroid infiltrations</td>
<td>Queiro et al</td>
</tr>
<tr>
<td>2</td>
<td>M/76 Caucasian</td>
<td>White-scaled plaques in the extensor extremities and scalp, nummular guttate macules on the trunk</td>
<td>NA</td>
<td>No</td>
<td>Mild arthritis involving hand and wrist joints with swelling if multiple digits</td>
<td>Etanercept 50 mg twice weekly. A twice-daily application of halobetasol ointment to the body, betamethasone valerate solution to the scalp, and calcipotriene solution to the scalp and body plaques</td>
<td>Dudelzak et al</td>
</tr>
<tr>
<td>3</td>
<td>M/60 Taiwanese</td>
<td>Multiple guttate white-scaled papules/plaques over the trunk, back, and four extremities</td>
<td>High grade</td>
<td>No</td>
<td>No fever or arthralgia was noted; relapsed after following BCG instillation</td>
<td>Narrow-band UV-B phototherapy. A twice-daily application of difucortolone valerate cream</td>
<td>Present case</td>
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</tbody>
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MCP = metacarpophalangeal; NA = not available; NSAIDs = non-steroidal anti-inflammatory drugs.


