Immunotherapy-related genital BCGitis: Case report and a review of histopathology

KEYWORDS: active immunotherapy, BCGitis, BCG vaccine, dermatopathology, granuloma

Immunotherapy with bacillus Calmette-Guérin (BCG) is widely used for superficial urothelial cancer treatment. The resulting granulomatous inflammation probably leads to the concomitant destruction of tumor cells. BCG, an attenuated strain of Mycobacterium bovis, remains viable, hence a potential for serious life-threatening complications exists. Most complications, however, are common, and include minor reactions such as cystitis, hematuria, fever, and malaise. Granulomatous inflammation of the penis with BCG intravesical therapy is reportedly rare. Clinical manifestations vary, as does the interval between immunotherapy sessions and lesion appearance. Penile edema, yellowish papules, ulceration, and abscesses have been described, and regional lymphadenopathies are common.

The local inoculation of the BCG is the main causal factor due to improper execution of the procedure (oftentimes citing trauma, ...

FIGURE 1 Papules, pustules, and a hemorrhagic crust on the glans penis (A); a distinct suppurative granuloma, composed of layers of epithelioid histiocytes without multinucleated giant cells, a central collection of neutrophils, and lymphocytes at the periphery H&E ×200 (B)
<table>
<thead>
<tr>
<th>Reference</th>
<th>Duration&lt;sup&gt;a&lt;/sup&gt; (days)</th>
<th>Inflammatory infiltrate as described</th>
<th>Necrosis&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Giant cells&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Other features</th>
<th>MB stains&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Culture&lt;sup&gt;e&lt;/sup&gt;</th>
<th>NATs&lt;sup&gt;f&lt;/sup&gt;</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Konohana, 1992&lt;sup&gt;15&lt;/sup&gt;</td>
<td>14</td>
<td>Granulomatous</td>
<td>Y</td>
<td>LT</td>
<td>Neutrophils</td>
<td>Neg (T)</td>
<td>Neg-MYC (U; BK (T))</td>
<td>–</td>
<td>Diagnosed as primary penile TB</td>
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<tr>
<td>Ribera, 1995&lt;sup&gt;10&lt;/sup&gt;</td>
<td>17</td>
<td>Tuberculoid granulomas &amp; dense lymphocytic</td>
<td>Y</td>
<td>LT</td>
<td>−</td>
<td>Neg (T)</td>
<td>MTBC (T)</td>
<td>MTBC (T)</td>
<td>−</td>
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<tr>
<td>Latini, 2000&lt;sup&gt;16&lt;/sup&gt;</td>
<td>−</td>
<td>Mixed and granulomatous</td>
<td>N</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>Penile shaft nodules</td>
</tr>
<tr>
<td>French, 2001&lt;sup&gt;5&lt;/sup&gt;</td>
<td>&gt;17</td>
<td>Granulomatous</td>
<td>Y</td>
<td>−</td>
<td>Neg (T)</td>
<td>Neg-MYC (U; T)</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Manikandan, 2003&lt;sup&gt;17&lt;/sup&gt;</td>
<td>−</td>
<td>Granulomatous</td>
<td>N</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
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<tr>
<td>Gemmel, 2004&lt;sup&gt;18&lt;/sup&gt;</td>
<td>&gt;180</td>
<td>Granulomatous and loose lymphocytic</td>
<td>Caseous</td>
<td>Y</td>
<td>−</td>
<td>Pos (U; S)</td>
<td>BCG (U; S)</td>
<td>−</td>
<td>Scrotal abscess; lung disease</td>
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<tr>
<td>Yusuke, 2006&lt;sup&gt;11&lt;/sup&gt;</td>
<td>−</td>
<td>Granulomatous</td>
<td>Y</td>
<td>LT</td>
<td>−</td>
<td>Neg (T)</td>
<td>−</td>
<td>−</td>
<td>Prostate lesions</td>
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<tr>
<td>Kureshi, 2006&lt;sup&gt;6&lt;/sup&gt;</td>
<td>30</td>
<td>Granulomatous</td>
<td>Y</td>
<td>−</td>
<td>Ulceration</td>
<td>Neg (T)</td>
<td>Neg-MYC (T)</td>
<td>−</td>
<td>Penile shaft nodules</td>
</tr>
<tr>
<td>Yates, 2007&lt;sup&gt;4&lt;/sup&gt;</td>
<td>−</td>
<td>Granulomatous</td>
<td>Y</td>
<td>−</td>
<td>−</td>
<td>Neg (T)</td>
<td>Neg-MYC (T)</td>
<td>−</td>
<td>−</td>
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<tr>
<td>Michelet, 2008 (A)&lt;sup&gt;6&lt;/sup&gt;</td>
<td>&gt;90</td>
<td>Granulomatous</td>
<td>Y</td>
<td>Y</td>
<td>Lymphocytes</td>
<td>Pos (T)</td>
<td>Neg-MYC (T)</td>
<td>−</td>
<td>−</td>
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<tr>
<td>Michelet, 2008 (B)&lt;sup&gt;6&lt;/sup&gt;</td>
<td>&gt;81</td>
<td>Granulomatous</td>
<td>Y</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>Neg-MYC (U; T)</td>
<td>Neg-BK (U; T)</td>
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</tr>
<tr>
<td>Yoshida, 2008&lt;sup&gt;19&lt;/sup&gt;</td>
<td>−</td>
<td>Granulomatous &amp; dense lymphocytic</td>
<td>Y</td>
<td>LT</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
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<tr>
<td>Hillyer, 2009&lt;sup&gt;20&lt;/sup&gt;</td>
<td>&gt;30</td>
<td>Granulomatous &amp; chronic inflammatory</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
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<tr>
<td>Lestre, 2011&lt;sup&gt;7&lt;/sup&gt;</td>
<td>90</td>
<td>Granulomatous</td>
<td>−</td>
<td>Y</td>
<td>Plasma cells; lymphocytes</td>
<td>Neg (T)</td>
<td>Neg-MYC (T)</td>
<td>−</td>
<td>−</td>
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<tr>
<td>Sharma, 2011&lt;sup&gt;21&lt;/sup&gt;</td>
<td>3</td>
<td>Granulomatous</td>
<td>−</td>
<td>LT</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
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<tr>
<td>Aslan, 2013&lt;sup&gt;22&lt;/sup&gt;</td>
<td>2</td>
<td>Granulomatous</td>
<td>−</td>
<td>Caseous</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Baldovi, 2013&lt;sup&gt;23&lt;/sup&gt;</td>
<td>2</td>
<td>Neutrophilic</td>
<td>N</td>
<td>N</td>
<td>Neutrophils</td>
<td>Neg (T)</td>
<td>BK (T)</td>
<td>−</td>
<td>−</td>
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<tr>
<td>Chowdhury, 2013&lt;sup&gt;24&lt;/sup&gt;</td>
<td>4</td>
<td>Granulomatous</td>
<td>Caseous</td>
<td>LT</td>
<td>Ulceration</td>
<td>Neg (T)</td>
<td>ND</td>
<td>−</td>
<td>−</td>
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<tr>
<td>Linden-Castro, 2014&lt;sup&gt;8&lt;/sup&gt;</td>
<td>−</td>
<td>Granulomatous</td>
<td>−</td>
<td>Central</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Shimura, 2017&lt;sup&gt;12&lt;/sup&gt;</td>
<td>−</td>
<td>Granulomatous</td>
<td>Y</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Present case</td>
<td>4</td>
<td>Suppurative granuloma</td>
<td>N</td>
<td>N</td>
<td>Neutrophil abscess</td>
<td>Neg (T)</td>
<td>Neg (T)</td>
<td>−</td>
<td>−</td>
</tr>
</tbody>
</table>

<sup>a</sup>Durations are given in time presumably elapsed since beginning of lesions and biopsy, as described in text.

<sup>b</sup>Necrosis: Y, yes; N, not present; −, not mentioned.

<sup>c</sup>Giant cells: LT, Langhans-type; Y, yes; N, not present; −, not mentioned.

<sup>d</sup>MB stains, mycobacterial stains: Neg, negative; Pos, positive; E, exudate; S, sputum; T, tissue; U, urine; UNSS, unspecified specimen.

<sup>e</sup>Culture: MYC, Mycobacterium spp. (or acid-alcohol resistant bacillus); MTBC, Mycobacterium tuberculosis complex; BK, Mycobacterium tuberculosis; BCG, Mycobacterium bovis; UNSIsolate, unspecified isolate.

<sup>f</sup>NATs, nucleic acid tests: MTBC, Mycobacterium tuberculosis complex; BK, Mycobacterium tuberculosis; BCG, Mycobacterium bovis.
spillage, or difficult catheterization). Inadvertent voidance of the instilled bladder content on the surrounding skin has also been implicated. In addition to a history of BCG instillation therapy, a local biopsy is often the sole procedure to collect evidence of the condition, before treatment initiation.

We recently observed a patient with immunotherapy-related genital BCGitis and decided to review the literature on its histological findings.

A 67-year-old Caucasian male patient was observed due to several papules on the glans penis, with 4 days duration. Owing to a high-grade, urothelial carcinoma in situ, he underwent transurethral bladder resection 4 months before presentation. He started BCG therapy approximately 4 weeks after surgery with a total of seven sessions. On the third session, the nurse-performed catheterization was reported as difficult and uncomfortable, and resulted in trauma to the urethral meatus. The patient subsequently reported fever, malaise, shaking, and trembling which subsided during the following week. Six weeks after, he progressively developed four painless erythematous papulo-pustules, on the surface of the glans (Figure 1A). No lymphadenopathies were present. The patient denied any systemic symptoms and other genito-urinary signs. Skin biopsy showed a nodular infiltrate of histiocytes with a central neutrophilic abscess (Figure 1B). Detection of acid-alcohol-resistant bacilli and culture were negative, and polymerase chain reaction (PCR) for mycobacteria was not performed. A diagnosis of penile BCGitis was made.

BCG immunotherapy was interrupted and the patient was treated with isoniazid 300 mg/day, rifampicin 600 mg/day and ethambutol 1200 mg/day (for 6 months). Residual hyperpigmentation remained on a follow-up visit 1 month later. No relapses have been observed after 12 months.

A literature search using PubMed (with the keywords: BCGitis, glans, penis, genital, and immunotherapy) rendered 21 papers. Two were excluded for lacking description of histology. The remaining address 20 different cases, to which we add our own (Table 1).

Almost all cases mentioned lesions on the glans or balanopreputial sulcus. Lymphadenopathy was very common. Involvement of other neighboring sites was mentioned in three cases, and disease at distant sites on the skin or on other organs in three cases. Immunotherapy-related BCGitis diagnosis was made based on clinical features supported by histology of skin lesions (n = 21); culture of tissue (n = 14), urine (n = 7), exudate (n = 2) or sputum (n = 2); and nucleic acid tests (NATs) of tissue (n = 6) or urine (n = 2).

Regarding histology, specimens were from the penile mucosa or skin in 20 cases, and from scrotal lesions in one case. Twenty (95%) cases reported granulomatous inflammation. Eighteen cases addressed the presence of necrosis, described as caseous in three and absent in the remaining three cases. Ten cases mentioned giant cells, eight of which described some as Langhans-type. Other features were occasionally referenced, such as neutrophils and plasma cells, fibrosis, granulation tissue, or necrosis. Besides our current observation, only one other mentioned a relevant neutrophilic infiltrate. Staining with Ziehl-Neelsen or auramine-rhodamine stains was mentioned in 16 instances, where positivity was found in penile tissue biopsy in only two occasions (12.5%).

Culture was inconsistently described in terms of cultured specimens, bacterial isolation, especially growth media used, and not mentioned or not performed in three instances. In 18 cases, cultured specimens were: tissue in 14 cases, urine in seven cases, and exudate and sputum in two cases, each. Isolation was possible in seven cases.

Finally, NATs were performed in seven instances (tissue, in six cases, and urine, in two cases). Positivity for Mycobacterium tuberculosis complex and for BCG was found in one case, each.

This study highlights that genital M. bovis-related inflammation is granulomatous in nature, with an infiltrate that is predominantly histiocytic and with frequent giant cells of Langhans type, as is common for tuberculous mycobacterial infections. Despite being frequently reported on, caseous necrosis may be absent. The presence of a significant neutrophilic infiltrate is possible, and we postulate that it may be related to lesion duration as part of the initial response to the inoculate. We tried to support this hypothesis by examining lesion duration at the time of biopsy, but this clearly insufficient number of cases precluded us from safely drawing a definite conclusion.

The overall results of our review highlight the importance of histologic examination for iatrogenic genital BCGitis diagnosis because culture and NATs yield inconsistent results. Detection of an infective agent is difficult (38% of cases in this literature series). Direct microscopic observation of bacilli was rare (9.5%). Culture results were inconsistently described as isolates of mycobacteria. NATs were scarcely reported on, and were conclusive on already “culture-positive” cases.

Because culture and NATs are scarcely reported and apparently produce inconsistent results, histology is also crucial for supporting the diagnosis of iatrogenic BCGitis. Without a clear clinical history the clinical differential diagnoses could include mainly infective conditions (e.g., herpes virus, syphilis, candida, other mycobacteria), and rarely tuberculids, or other inflammatory conditions (e.g., psoriasis, pyoderma, or Behçet disease). For most of these, a clear-cut granulomatous dermal inflammation will disfavor the diagnosis.

In conclusion, iatrogenic penile BCGitis is mainly responsible for a granulomatous inflammation, although a predominantly or mixed neutrophilic infiltrate is possible, as seen in this case. Clinical-pathologic correlation is of paramount importance, because microbiological tests may be negative.

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REFERENCES


