

Figure 1

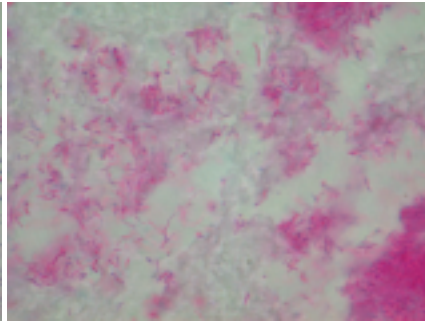


Figure 2

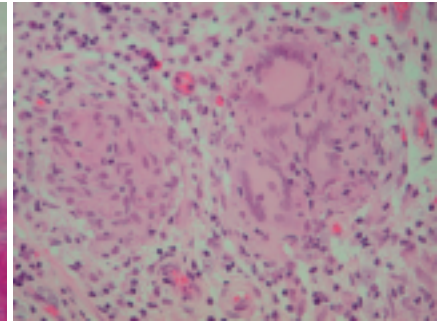


Figure 3

1. What do the figures show?
2. Why do these lesions form?
3. What is the therapeutic significance of the process and how does it work?
4. What complications may arise from this therapy?

The figures show granulomatous inflammation of bladder mucosa (Figure 1) following intravesical instillation of *Bacillus Calmette-Guérin* (BCG; Figure 2), a live, attenuated strain of *Mycobacterium bovis*. BCG is used as a vaccine to induce anti-tumour effects, most successfully in certain types of bladder neoplasm.

Granulomatous inflammation is a form of chronic inflammation. The latter varies in its histopathological appearances and results either from the persistence of a relatively inert stimulus (eg. foreign body granuloma related to a surgical suture) or when an immunological reaction is evoked. Mycobacteria infect naïve macrophages and can survive and replicate within their phagosomes. When the patient develops specific immune mechanisms, T-lymphocytes stimulate macrophages to kill their intracellular burden of mycobacteria. This also leads to the formation of granulomas. BCG granulomas consist of epithelioid cells (activated macrophages), Langhans-type giant cells, and lymphocytes (Figure 3). Other types of inflammatory cell (eg. plasma cells) may be found nearby.

BCG immunotherapy is commonly used to treat superficial transitional cell neoplasms of the bladder that are at risk of recurrence or progression: carcinoma in situ (CIS); non-invasive high-grade papillary tumours (G3, pTa) or those that are multifocal or have recurred rapidly; and cases showing invasion of the lamina propria (pT1). It is effective in reducing both the recurrence rate and the risk of progression of the neoplasm, particularly if a maintenance regime is used after the initial induction course.

The success of intravesical BCG therapy is a fascinating immunological feat. The mechanisms have not been fully elucidated, but the immune responses can be identified from the analysis of cytokines and immune cells. Urine analysis post-BCG therapy reveals many cytokines, including interleukin (IL)-2, IL-12, interferon γ (INF γ), and tumour necrosis factor α (TNF α), among others. Lymphoid cells, such as helper (CD4+) and cytotoxic (CD8+) T-cells, lymphokine-activated killer cells (LAKs), BCG-activated killer cells (BAKs), and macrophages accumulate within the bladder mucosa. These components implicate immune mechanisms, such as the cell-mediated immune response and natural killer cell lysis.

Before a cell-mediated immune response can occur, the mycobacteria bind to fibronectin molecules of the extracellular matrix. Professional antigen-presenting cells (APCs) - monocytes, macrophages and dendritic cells - phagocytose the bound bacteria and present bacterial antigens at their surfaces associated with the cells' major histocompatibility complex (MHC) class II molecules. Co-stimulatory factors, including the release of IL-12 by the activated APCs, initiate the binding and activation of CD4+ lymphocytes. The CD4+ cells then release IL-2 and INF γ , inducing proliferation of other CD4+ cells and activation of macrophages, respectively. INF γ -activated macrophages promote intracellular mycobacterial killing. Waxy components of the bacterial cell wall are poorly degraded, contributing to the formation of BCG granulomas. Interestingly, urothelial cells, particularly those derived from high-grade transitional cell neoplasms, can also take up BCG. This may be important in the therapeutic effect through several different mechanisms.

Specific lysis of tumour cells occurs by sensitised cells, such as LAKs and BAKs. IL-2 release appears to stimulate LAK generation, while the introduction of BCG induces the proliferation of specific BAKs. Both killer cells share a common lysis mechanism: intracellular perforin is exocytosed and polymerises in the presence of Ca²⁺ ions to form channels in the tumour cell surface membrane. Cytotoxic enzymes released from the killer cells then enter the tumour cells via these perforin channels, causing tumour cell lysis. TNF- γ released by the activated macrophages has an inhibitory effect on vascularisation, thereby potentially reducing blood supply to tumour tissue.

BCG therapy requires a normally functioning immune system. It is contraindicated in patients who are immunocompromised because of congenital deficiency, acquired disease (including HIV infection), or therapy. Some degree of cystitis is inevitable in BCG therapy but it is usually mild and often does not require treatment. With cumulative treatment, the risk of developing a flu-like syndrome with fever and malaise increases, presumably due to the release of immune mediators. Rarer complications include arthritis or arthralgia, skin rash, granulomatous epididymitis or prostatitis, ureteric obstruction, bladder contraction, or potentially life-threatening systemic infection. The mechanisms of action of BCG immunotherapy need further elucidation. Future developments may allow better targeting of treatment to enhance clinical efficacy and reduce side-effects.

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Further reading

1. Bevers RFM, Kurth K-H, Schamhart DHJ. *Role of urothelial cells in BCG therapy for superficial bladder cancer.* Br J Cancer 2004;91:607-12.
2. Böhle A, Brandau S. *Immune mechanisms in Bacillus Calmette-Guérin immunotherapy for superficial bladder cancer.* J Urol 2003;170:964-9.

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