

Cryoglobulinemia vasculitis following intravesical instillations of bacillus Calmette-Guérin

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ABSTRACT

Infections and/or immune-mediated reactions may occur after intravesical instillation of bacillus Calmette-Guérin for the treatment of bladder carcinoma. We report herein a cryoglobulinemia vasculitis occurring after intravesical BCG instillation for a superficial papillary transitional cell bladder carcinoma. The patient, an 80-year-old man, presented peripheral ischemia 10 days after the second course of intravesical BCG instillation. Biological evaluation revealed autoimmune thrombocytopenia, hypergammaglobulinemia, low C3 and C4 complement fraction levels related to mixed cryoglobulinemia and lupus anticoagulant. The patient was treated with heparin and prostacyclins with a good outcome. All of the immune anomalies spontaneously regressed within 3 months. To our knowledge, cryoglobulinemia has only been reported once in the literature and lupus anticoagulant has never been reported as a complication of intravesical BCG instillation.

Introduction

Intravesical instillation of bacillus Calmette-Guérin (BCG) immunotherapy is an effective treatment for the management of recurrent superficial transitional cell carcinoma and *in situ* carcinoma of the bladder. As a live attenuated strain of *Mycobacterium bovis* is used, complications can occur and are related to the infective agent or to an immune mediated reaction. We report an exceptional case of cryoglobulinemia vasculitis associated with lupus anticoagulant and autoimmune thrombocytopenia after intravesical BCG instillation.

Case report

An 80-year-old man suffered in January 2001 from a superficial papillary transitional cell bladder carcinoma. Treatment included endoscopic resection and intravesical BCG therapy. On April 11, 2001, he received the second instillation of intravesical BCG after an uneventful first instillation on March 27, 2001. Ten days later he had high fever (39°C) and pain in both hands and feet and rapidly sought a consultation. Physical examination revealed

peripheral ischemia with coldness and cyanosis of the fingers and toes. Ischemic lesion was particularly severe in the fifth finger of the left hand and was associated with necrosis. Peripheral pulses were all present. There were purpuric lesions and skin erythema on the trunk and lower limbs. No polyarthralgia was noted.

Biological evaluation showed a normal white blood cell count, a haemoglobin level of 135 g/L and a platelet count of $95 \times 10^9/L$. The erythrocyte sedimentation rate was 11 mm/h and C-reactive protein was 23 mg/L ($N < 5$). Serum protein electrophoresis revealed a moderate oligoclonal increase of immunoglobulins (Ig) G (IgG level of 19 g/L ($N: 7-14$)). Proteinuria was 0.286 g/24h, without Bence Jones protein. There was a low C3 level of 0.35 g/L ($N: 0.82-1.58$) and a low C4 level of 0.10 g/L ($N: 0.10-0.34$). Mixed type II cryoglobulinemia was observed with a IgG lambda monoclonal component.

A search for anti-platelet autoantibodies was strongly positive and bone marrow aspiration showed normal megakaryocytes with 3% plasma cells. A search for cold agglutinins was negative. There was no antinuclear, anti-DNA, or anti-extract cell tissue and there were no antineutrophil cytoplasmic antibodies. Serological tests for hepatitis C and B viruses and HIV were negative. There was a lupus anticoagulant with Rosner index of 44 ($N: < 12$), without anti-cardiolipin and anti-beta2-glycoprotein I (IgG and IgM isotypes) antibodies. Protein S and protein C levels were normal, and mutations in the factor II and V genes were absent. HLA typing was A25, A32, B44, B51, and DRB1*11, DRB1*12.

Arterial ultrasonography of the upper and lower limbs, thoraco-abdominal CT-scan and transoesophageal echocardiography were normal. Treatment with intravenous heparin and prostacyclin led to clinical improvement except for the fifth finger of the left hand, which required partial amputation. Anti-tuberculosis therapy was not given, as there was no fever and no sign of *M. bovis* infection. Three months after symptom onset, the patient felt healthy with a normal platelet count, normal

complement fractions and disappearance of the lupus anticoagulant and cryoglobulinemia.

Discussion

BCG immunotherapy instillations are well tolerated by most patients and more than 95% do not experience significant adverse events (1-4). Systemic manifestations are rare and concern less than 1% of patients (1-3). The main clinical symptom is fever, frequently associated with arthralgia or migratory arthritis (1,2). The predominance of articular symptoms can be explained by the cross-reactivity ("molecular mimicry") shared by mycobacterial antigens, particularly the "heat shock protein antigens", and human cartilage (3). Usually synovial fluid and blood cultures for mycobacteria remain sterile (5, 6). Other systemic complications include BCG sepsis (0.4% of patients) which constitutes the most serious life-threatening complication (2, 3, 7). This infection usually results from the intravenous absorption of bacteria through an inflamed or disrupted bladder wall (2, 3). Thus, systemic side effects after BCG immunotherapy can be related to an ongoing infection or to a hypersensitivity response.

Cryoglobulinemia after intravesical administration of BCG has been reported, to our knowledge, only once by Durand *et al.* (8). The patient had a purpuric rash on both legs with leukocytoclastic vasculitis on cutaneous biopsy. A monoclonal gammopathy of IgM kappa, a type II cryoglobulinemia and anticardiolipin antibodies were noted. Cryoglobulinemia has frequently been observed after viral infections, particularly after hepatitis virus C infection (9) or hepatitis B vaccination (10), but only a few reports of cryoglobulinemia related to *M. tuberculosis* infection have been made (11, 12). In our patient serological tests for hepatitis B and C

viruses were negative. Cryoglobulinemia could have been induced by the immune stimulation as a consequence of antigen loading in relation to the haematogenous spread of BCG from the bladder. Normally intravesical BCG instillations increase the local immune response with the aim of eliminating the tumor. Therefore, since BCG can affect the immune system at least locally, it might also affect it systemically when there is a haematological spread.

We feel that the immune anomalies observed in this patient (cryoglobulinemia, lupus anticoagulant and thrombocytopenia) were induced by a hypersensitivity response and were not directly related to the spread of an active infectious process. Moreover, all these anomalies spontaneously regressed without anti-tuberculosis treatment. A hypersensitivity response was also suggested in the recently published case of a Sjögren's-like syndrome following intravesical BCG immunotherapy (13). Animal models provide additional support for the hypersensitivity hypothesis. In experiments performed on NZB/NZW hybrid mice, treatment with the *M. bovis* strain has been shown to accelerate the autoimmune disease (14). As observed in mice, the genetic background is known to play an important role. Reactive arthritis following intravesical BCG instillation is frequently associated with HLA-B27 (about 60% of cases) (15). Our patient was not HLA-B27 positive and this could explain the absence of articular symptoms.

This case illustrates the risk of immune anomalies after intravesical BCG. In our patient, lupus anticoagulant and cryoglobulinemia could have induced the peripheral vascular ischemia.

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