

Polymyalgia rheumatica following intravesical bacillus Calmette-Guerin instillation: coincidence or true association? A case report and literature review

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Abstract

We report the case of a 73-year-old male patient suffering from non muscle invasive bladder cancer (NMIBC) who had violent pains in his neck and shoulders associated with general discomfort and fever, following the second intravesical instillation of bacillus Calmette-Guerin (BCG), with further worsening after the third instillation. During his hospitalization, laboratory tests showed a significant raise of inflammatory markers. An ultrasound (US) examination of his shoulders showed bilateral longhead-biceps exudative tenosynovitis and subdeltoid bursitis. An 18-fluorodeoxyglucose positron emission tomography (18-FDG PET) associated with total body computed tomography (CT) showed pathological inflammatory findings in neck and shoulders, with exclusion of pathological findings in other sites. Cystoscopy was negative for NMIBC recurrence. Polymyalgia rheumatica (PMR) was diagnosed and BCG instillations was stopped. The patient had fast improvement of clinical manifestations and laboratory tests, but when he resumed them a few weeks later, the same manifestations recurred.

Introduction

Polymyalgia rheumatica (PMR) is considered the most frequent inflammatory rheumatic disease in Caucasians over the age of 70 years.¹⁻³ Its diagnosis is based upon recognition of a clinical syndrome consisting of pain localized to neck and shoulder and pelvic girdles, associated with morning stiffness of inflammatory type (*i.e.* lasting more than 45 minutes). In some PMR patients, constitutional manifestations such as weight loss, fever of unknown origin, general discomfort, fatigue, and loss of appetite complete the clinical picture.^{4,5} To date, no specific laboratory tests are available. Erythrocyte sedimentation rate (ESR)

and C-reactive protein (CRP) concentrations are usually raised at the time of diagnosis, but normal ESR and CRP should not be a reason of exclusion for PMR.^{6,7} Shoulder and hip ultrasound (US) examinations can give important contributions, as proposed by 2012 EULAR/ACR classification criteria. This EULAR/ACR collaborative initiative also highlighted that prednisone response is not reliable as a classification feature for PMR.⁸ The etiopathogenesis of PMR is still debated. Some infectious and environmental agents have been suggested as triggers, but data are mostly anecdotal.⁹

Intravesical instillation of bacillus Calmette-Guerin (BCG) after transurethral resection (TUR) is considered the gold-standard treatment for non-muscle invasive bladder cancer (NMIBC), at high risk of recurrence or progression.¹⁰ BCG attachment to fibronectin present at the endoluminal layer, its internalization into resident immune cells, normal cells, and tumour urothelial cells, and the next induction of innate and tumour-specific immunity, are significant steps of this immunotherapy. The final result is the destruction of the neoplastic cells.¹¹

Case Report

In 2015, a 73-year-old male patient affected with NMIBC complained of violent pains in his neck and shoulders associated with general discomfort and fever, after the second endovesical instillation of BCG. The intake of acetaminophen determined fever resolution, and transient relief of pain. After the third instillation, pains in scapular girdles and neck worsened to the point that he was totally dependent on family members in daily life activities. During hospitalization, the laboratory tests showed: ESR = 52 mm/h; CRP concentration = 30 mg/dL (normal value <6). In the normal ranges were: serum fibrinogen levels, rheumatoid factor (RF) and anti-protein citrullinated antibodies (APCA), hemoglobin, transaminases, creatine phospho kinase, protein electrophoresis, antinuclear cytoplasmic antibodies (ANCA). Urinoculture and urine blood test were negative. Occult blood research in the stool was negative and fecal calprotectin dosage was in its normal range. Antibodies to hepatitis C virus and Australia antigen were absent. Cystoscopy showed normal findings. An US examination showed bilateral long-head-biceps exudative tenosynovitis and subdeltoid bursitis in his shoulders. 18-FDG PET/CT showed inflammatory findings in neck and

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Informed consent: a written informed consent for publication was obtained from the patient. The author declares full availability to show this informed consent, according to Italian privacy policy.

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shoulders, with exclusion of pathological findings in other sites. According to 2012 ACR/EULAR criteria (total score of 8 in our patient), PMR was considered. His urologist advised to stop cautiously BCG endovesical instillations. In just a few days, the patient had a rapid improvement of pain and restored full autonomy. ESR and CRP normalized after 10 and 3 days, respectively. When he resumed the endovesical instillations of BCG a few weeks later, the same manifestations recurred and it was decided to stop them definitively.

During a follow up of 4 years, all PMR-mimicking diseases were excluded (Table 1), and no alternative diagnosis was possible. Temporal artery color duplex sonography (TA-CDS), 18-FDG-PET with total body contrast-enhanced computed tomography (CT) and cystoscopy showed normal findings every time when the study was conducted.

Discussion

An involvement of joints, with the clinical pattern of reactive arthritis, is a well-known side effect of intravesical BCG immunotherapy. By far, the large joints of lower limbs are the most involved and the

Table 1. Main diseases with which PMR is in differential diagnosis, and signs and symptoms useful for a correct diagnosis.

Disease	Signs and symptoms useful for a correct diagnosis
Rheumatoid arthritis	Involvement of some joints of the hands (metacarpophalangeal II and III, and proximal interphalangeal), positive results of rheumatoid factor and anti-cyclic citrullinated peptide antibodies (ACPA), radiographic and ultrasound findings (erosive arthritis, periarticular osteoporosis)
Remitting Seronegative Symmetrical Synovitis with Pitting Edema (RS3PE)	Symmetric multiple synovitis, seronegative in rheumatoid factor and ACPA, causing boxing-glove swelling with pitting edema of hands and feet. Ultrasound findings: tenosynovitis of extensor tendon sheath
Late-onset spondyloarthropathies, including ankylosing spondylitis and psoriatic arthritis	Inflammatory pain in the lumbar region; radiographic findings of sacroiliitis; psoriasis
Late-onset systemic lupus erythematosus, scleroderma, Sjogren's syndrome, vasculitis	Inflammatory pain in the lumbar region; radiographic findings of sacroiliitis; psoriasis
Late-onset systemic lupus erythematosus, scleroderma, Sjogren's syndrome, vasculitis	Presence of antinuclear antibodies, presence of antineutrophil cytoplasmic antibodies
Idiopathic inflammatory myopathies (dermatomyositis, polymyositis)	Skin rashes, increased creatine kinase in the blood
Scapulohumeral periartthritis, adhesive capsulitis (<i>frozen shoulder</i>)	Restriction of shoulder movements, even in passive; ultrasound and magnetic resonance imaging allow one to diagnose the specific inflammation. Inflammatory markers not raised
Calcium pyrophosphate deposition disease	Monoarthritis; radiographic and ultrasound findings
Paraneoplastic syndromes	Failure to respond to glucocorticoid therapy or frequent relapses must be considered as elements of suspicion. Furthermore, the presence of untypical clinical manifestations and of laboratory findings (among these, macrocytic anemia or bicytopenia), and familiarity for neoplasms should also be considered as warning
Fibromyalgia	Inflammatory indices in their normal range, presence of tender points, widespread chronic pain
Reactive arthritis	Inflammatory back pain, additive or migratory oligoarthritis, presence of extra-articular symptoms, following a gastrointestinal or urogenital infection by a minimum of 1 to a maximum of 3-6 weeks. Long-term corticosteroid therapy is not required

asymmetry is the prevalent pattern. Arthritis usually has a self-limiting course with poor tendency to chronicity. The involvement of shoulder and pelvic girdles, typical of PMR, has never been described during BCG-reactive arthritis.¹² A definite genetic link is documented by human leucocyte antigens (HLA) B27 carriers in about half cases, supporting the hypothesis that, at least in these patients, the failure of immunological tolerance in association with the presence of BCG in the bladder can lead to an immunmediate inflammatory reaction in the joints.¹³

Quite recently, we reported the case of a 69-year-old male patient suffering from PMR and remitting seronegative symmetrical synovitis with pitting edema (RS3PE), which occurred after a cycle of six intravesical instillation of BCG. In this patient, prednisone therapy was necessary for full resolution of PMR.¹⁴

According to literature review, only a case of PMR associated with giant cell arteritis (GCA)¹⁵ and a case of isolated GCA¹⁶ have been reported. PMR and GCA are closely related and often overlapping conditions. In some patients, PMR may be the presenting manifestation of GCA. In addition to this, some investigators speculated that PMR might be an incomplete

form of GCA, manifested in the proximity of axillary, subclavian, and/or femoral arteries.¹⁷ In our patient, diagnosis of GCA was clinically excluded at the time of diagnosis of PMR, and during follow-up using TA-CDS and 18-FDG PET/CT imaging.

The possibility that PMR may be a paraneoplastic syndrome has been widely discussed in the literature, with contrasting point of views. Bladder cancer can be diagnosed in the first year after the diagnosis of PMR.^{18,19} Therefore, the possibility that in our patient PMR could be a paraneoplastic finding was carefully excluded.

As for today, the reasons why in our patient PMR followed BCG immunotherapy for NMIBC are only speculative. According to the so-called *molecular mimicry theory*, the shared homology between BCG proteins such as heat-shock protein HSP65 and juxtasyovial proteins located in shoulder and/or pelvic girdles could play a relevant role. Genetic factors, related to major histocompatibility complex (MHC) class I, could be another favoring factor, acting as restriction molecules for antigenic bacterial peptides presented to and cross recognized by cytotoxic CD8+ T lymphocytes. Furthermore, these peptides possess a potential to skew the immune response

toward Th1-like patterns.²⁰ The senescence of the immune system as demonstrated by the loss of CD28 on CD4+ T senescent cells may be an additional responsible factor in patients with PMR, leading to aberrant immune responses.⁹

Conclusions

According to literature review, the occurrence of PMR during BCG intravesical instillations is very rarely described, despite the widespread use of this immunotherapy.

In our patient, its rapid disappearance after BCG instillations and its prompt reappearance after their re-introduction suggest that PMR has been a true association with this immunotherapy, and not a coincidence.

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