Polymyalgia rheumatica and remitting seronegative symmetrical synovitis with pitting edema following intravesical instillation of bacillus Calmette-Guerin

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Abstract
Intravesical instillation of bacillus Calmette-Guerin (BCG) after transurethral cancer resection is an approved part of the management of non-muscle invasive bladder cancer (NMIBC). The onset of polymyalgia rheumatica (PMR) and remitting seronegative symmetrical synovitis with pitting edema (RS3PE) following this immunotherapy is anecdotal. We report the case of a 69-year-old male patient suffering from boxing-glove swelling of the hand associated with bilateral pain, aching and stiffness in the shoulders and pelvic girdles, which occurred after a cycle of six intravesical instillations of BCG. Polymyalgia rheumatica associated with RS3PE was diagnosed, prednisone therapy started and definitively stopped after 13 months. During a 16-year follow-up, no alternative diagnosis was possible. The role of genetic factors and of the senescence of the immune system is discussed. According to our best knowledge, this is the first case report of PMR associated with RS3PE following intravesical instillation of BCG.

Key words: immunotherapy, polymyalgia rheumatica, bacillus Calmette-Guerin, remitting seronegative symmetrical synovitis with pitting edema.

Introduction
According to the definition, polymyalgia rheumatica (PMR) affects people older than 50 [1, 2]. To date, in absence of a specific diagnostic test, its diagnosis is based on recognition of a clinical syndrome consisting of pain and stiffness in the shoulder and pelvic girdle, associated with morning stiffness lasting at least 45 minutes. PMR-mimicking diseases must be excluded [3–5]. Elevation of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) concentrations is the rule at the time of diagnosis, but normal ESR and CRP should not be a reason for exclusion of PMR [6].

The etiopathogenesis of PMR is still debated. Human leucocyte antigens (HLA) and some cytokines such as interleukin 6 (IL-6) have been particularly investigated, where the role of triggers is hazier. Indeed, several infectious and environmental agents have been suggested, but data in the literature are mostly anecdotal and should be confirmed on large cohorts [7].

Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) is an uncommon elderly-onset disease characterized by tenosynovitis of extensor tendons at the wrist and (less frequently) at the feet [8]. Its etiopathogenesis still remains unknown. Cytokines such as vascular endothelium derived growth factor (VEGF) and IL-6, and genetic factors (HLA-B7, HLA-A2, HLA-Cw7) are considered important in the development of RS3PE [9].

It is estimated that no more than 10% of patients with PMR may have RS3PE as an accompanying or an initial manifestation [10]. Both PMR and RS3PE may be paraneoplastic syndromes [9, 11], and the possibility that the association of PMR with RS3PE may be a neoplastic warning has been previously highlighted [12, 13]. The onset of PMR and RS3PE in cancer patients treated with immune checkpoint blockade has been reported [14–17].
Case report

In 2002, a 69-year-old male patient suffering from non-muscle invasive bladder cancer (NMIBC) developed a boxing-glove swelling of the right hand (Fig. 1) associated with bilateral pain, aching and stiffness in the shoulders and pelvic girdles. About a month earlier, the patient had finished a cycle of six intravesical instillations of bacillus Calmette-Guerin (BCG). According to McCarthy’s criteria [8] and Healey’s criteria [18], RS3PE associated with PMR was diagnosed.

After starting therapy with 10 mg of prednisone, the patient noticed that the swelling of the hand was completely disappeared, and there was a significant improvement of pain and functional impairment of the girdles. After 10 days, prednisone was stopped but symptoms such as bilateral pain and stiffness in the girdles quickly returned, whereas the swelling of the hand did not. A short hospitalization was arranged. Table I summarizes the patient’s medical data at the time of admission to the hospital and during hospitalization.

Therapy with 16 mg methylprednisolone was started. After a month, the patient spontaneously stopped methylprednisolone, but the manifestations reappeared, and the patient returned to the treatment with glucocorticoids. Methylprednisolone was gradually tapered and definitively stopped after 13 months of treatment. The described patient was observed and had follow-up examinations for the next 16 years due to concurrent cognitive impairment. In this period, there was no recurrence of PMR or RS3PE; peripheral arthritis was absent. Temporal artery color duplex sonography (TA-CDS) and 18-fluorodeoxyglucose positron emission tomography (18-FDG-PET) with total body contrast-enhanced computed tomography (CT) showed normal findings every time when the study was conducted.

Recently, the patient’s legal representative consented to publish the present case report.

Discussion

Since 1976, intravesical instillation of BCG after transurethral cancer resection has been an approved part of the management of NMIBC [19, 20]. Joint disease described as arthritis or arthralgia was found in 0.5% of 1278 patients treated with bacillus Calmette-Guerin immunotherapy in a retrospective review [21]. In a systematic review, 89 patients developed reactive arthritis following BCG immunotherapy, but, what is interesting, the shoulders were never affected [22].

The possibility that PMR and RS3PE may follow intravesical instillation of BCG is anecdotal. According to our best knowledge, only two cases of isolated RS3PE [23, 24] and one case of PMR associated with giant cell arteritis (GCA) [25] have been reported in the literature as associated with such therapy. An isolated GCA was recently reported in a patient with NMIBC [26]. No cases of PMR associated with RS3PE have been reported following BCG immunotherapy.

Polymyalgia rheumatica may be a paraneoplastic syndrome [11] and bladder cancer can be diagnosed in the first year after the diagnosis of PMR [11, 27]. In our patient, we found neither a recurrence of the bladder cancer nor a paraneoplastic syndrome.

Polymyalgia rheumatica and GCA are closely related and often overlapping conditions and, in some cases, PMR may be the presenting manifestation of GCA [28]. Some investigators speculated that PMR might be an incomplete form of GCA, manifested in the regions in the proximity of axillary, subclavian, and/or femoral arteries [29]. In our patient, diagnosis of GCA was clinically excluded at the time of diagnosis of PMR, and during the long follow-up using TA-CDS and 18-FDG PET/CT imaging.

As for today, the reasons why PMR associated with RS3PE follows the immunotherapy with BCG for NMIBC are speculative.

![Fig. 1. Boxing-glove swelling with pitting edema of our patient’s right hand.](image-url)
According to the so-called “molecular mimicry theory”, the shared homology between BCG proteins such as heat-shock protein HSP65 and synovial or juxta-synovial proteins might be very important. Genetic factors, related to HLA antigens, 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 [30].

The frequent positivity of HLA-B27 in reactive arthritis to BCG confirms the importance of genetic factors. In our patient, HLA-B27 was negative and other HLAs were not investigated.

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 [7].

Lastly, the pathogenetic role of some cytokines that are involved in PMR, RS3PE and cancer (IL-6, for example) remains to be proven.

Conclusions

Among the possible musculoskeletal manifestations following intravesical instillation of BCG, the onset of PMR and RS3PE is very rarely reported. According to our best knowledge, this is the first case report in which PMR is present together with RS3PE in a cancer patient following this immunotherapy. Instead, separate cases with occurrence of RS3PE or PMR following BCG instillation have both been rarely described.

The reasons why this happens are only speculative. Genetic factors and the senescence of the immune system seem to be the most significant factors.

In cancer patients such as patients with NMIBC, the possibility that the association RS3PE + PMR may be a paraneoplastic finding must be carefully investigated and excluded.

So far, shoulder involvement in BCG-reactive arthritis has not been reported. In clinical practice, this observation may be an important element for differentiating the diagnosis.

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Table I. Medical data of our patient

| ESR: 56 mm/h |
| CRP concentration: 60 vs. < 6 mg/dl |
| RF: normal range |
| ACPA: normal range |

Microbiological examination of SBD fluid: absence of BCG

- HLA-B27: negative
- Microbiological examination of SBD fluid: absence of BCG
- Total body CT: absence of pathologic findings

US examination: bilateral long-head-biceps exudative tenosynovitis and sub-deltoid bursitis (SDB) in his shoulders; trochanteric bursitis in his right hip

Cystoscopy: negative

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