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

Ciro Manzo
Azienda Sanitaria Locale Napoli 3 sud, Sant’Agnello, Napoli, Italy

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 long-head-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 were 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.

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 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 the lower limbs are the most involved and the
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. 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 immunomediately inflammatory reaction in the joints.

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 instillations of BCG. In this patient, prednisone therapy was necessary for full resolution of PMR.

According to literature review, only a case of PMR associated with giant cell arteritis (GCA) and a case of isolated GCA 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. 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. 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 juxtasynovial 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.

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.

### 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.

### References

1. Partington R, Helliwell T, Muller S, et al. Incidence, prevalence and treatment burden of polymyalgia rheumatica in the UK over two decades: a population...
study. Arthritis Res Ther 2018;20:258.
2. Crowson CS, Matteson EL. Contemporary prevalence estimates for giant cell arteritis and polymyalgia rheumatica, 2015. Semin Arthritis Rheum 2017;47:253-6.
2. Manzo C. Incidence and prevalence of polymyalgia rheumatica (PMR): the importance of the epidemiological context. The Italian case. Med Sci (Basel) 2019;7:pii:E92.
3. Milchert M, Brzosko M. Diagnosis of polymyalgia rheumatica usually means a favourable outcome for your patient. Indian J Med Res 2017;145:593-600.
4. González-Gay MA, Matteson EL, Castañeda S. Polymyalgia rheumatica. Lancet 2017;390:1700-12.
5. Manzo C, Milchert M, Natale M, Brzosko M. Polymyalgia rheumatica with normal values of both erythrocyte sedimentation rate and C-reactive protein concentration at the time of diagnosis. Rheumatology (Oxford) 2019;5:921-3.
6. Manzo C, Milchert M. Polymyalgia rheumatica with normal values of both erythrocyte sedimentation rate and C-reactive protein concentration at the time of diagnosis: A four-point guidance. Reumatologia 2018;56:1-2.
7. Dasgupta B, Cimmino MA, Kremers HM, et al. 2012 provisional classification criteria for polymyalgia rheumatica: A European League Against Rheumatism/American College of Rheumatology collaborative initiative. Arthritis Rheum 2012;64:943-54.
8. Guggino G, Ferrante A, Macaluso F, et al. Pathogenesis of polymyalgia rheumatica. Reumatismo 2018;70:10-7.
9. Babjuk M, Bohle A, Burger M, et al. EAU guidelines non-muscle-invasive urothelial carcinoma of the bladder: update 2016. Eur Urol 2017;71:447-61.
10. Pettenati C, Ingersoll MA. Mechanisms of BCG immunotherapy and its outlook for bladder cancer. Nat Rev Urol 2018;15:615-25.
11. Liu Y, Lu J, Huang Y, Ma L. Clinical spectrum of complications induced by intravesical immunotherapy of bacillus Calmette-Guerin for bladder cancer. J Oncol 2019;3.
12. Bernini L, Manzini CU, Giuggioli D, et al. Reactive arthritis induced by intravesical BCG therapy for bladder cancer: our clinical experience and systematic review of the literature. Autoimmun Rev 2013;12:1150-9.
13. Genereau T, Koeger AC, Chaibi P, Bourgeois P. Polymyalgia rheumatica with temporal arteritis following intravesical Calmette-Guerin bacillus immunotherapy for bladder cancer. Clin Exp Rheumatol 1996;14:110.
14. Stavris C, Retornaz F, Charpin C, et al. Vascularites des gros vaisseaux induites par une prise médicamenteuse: 2 nouveaux cas secondaires à l’administration de BCG-thérapie et de G-CSF. Rev Med Int 2016;37:A179.
15. Marzo-Ortega H, McGonagle D, O’Connor P, et al. Subclinical vasculitis in polymyalgia rheumatica. Ann Rheum Dis 2001;60:1058-9.
16. Manzo C. Polymyalgia rheumatica and remitting seronegative symmetrical synovitis with pitting edema following intravesical instillation of bacillus Calmette-Guerin. Reumatologia 2019;57:249-52.
17. Manzo C, Natale M. Polymyalgia rheumatica and cancer risk: the importance of the diagnostic set. Open Access Rheumatol 2016;8:93-5.
18. Muller S, Hider S, Helliswell T, et al. The real evidence for polymyalgia rheumatica as a paraneoplastic syndrome. Reumatismo 2018;70:23-34.
19. Pahari S, Deepayan Chatterjee D, Negi S, et al. Morbid sequences suggest molecular mimicry between microbial peptides and self-antigens: a possibility of inciting autoimmunity. Front Microbiol 2017;8:1938.