

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

Ciro Manzo

Center for Cognitive Impairment and Dementias, Azienda Sanitaria Locale Napoli 3 sud, Pomigliano d'Arco, Italy
Internal and Geriatric Medicine Department, Rheumatologic Outpatient Clinic Hospital "Mariano Lauro", Sant'Agnello, Italy

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 suggest-

ed, 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].

Address for correspondence:

Ciro Manzo, Center for Cognitive Diseases and Dementias, Azienda Sanitaria Locale Napoli 3 sud, 80038 Pomigliano d'Arco, Italy,
e-mail: cirmanzo@libero.it

Submitted: 2.06.2019; Accepted: 25.07.2019

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 arteritis [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.

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.

Acknowledgements

The author thanks Dr. Catello Esposito, head of the Internal Medicine Department of “Villa Stabia” clinic in Castellammare di Stabia, for his valuable collaboration, and Dr. Gian Luca Erre, rheumatologist of the University Hospital of Sassari, for some useful suggestions.

The author declares no conflict of interest.

Table I. Medical data of our patient

ESR: 56 mm/h
CRP concentration: 60 vs. < 6 mg/dl
RF: normal range
ACPA: normal range
Uricemia, serum fibrinogen levels, transaminases, creatine phosphokinase, protein electrophoretic mobility, ANCA, IgM-IgA-IgG serum concentrations: normal range
US examination: bilateral long-head-biceps exudative tenosynovitis and sub-deltoid bursitis (SDB) in his shoulders; trochanteric bursitis in his right hip
Cystoscopy: negative
Total body CT: absence of pathologic findings
Microbiological examination of SBD fluid: absence of BCG HLA-B27: negative

ESR – erythrocyte sedimentation rate, CRP – C-reactive protein, RF – rheumatoid factor, ACPA – anti-citrullinated protein antibodies, ANCA – anti-neutrophil cytoplasmic antibodies, Ig – immunoglobulins, US – ultrasound, CT – computed tomography, BCG – bacillus Calmette-Guerin, HLA – human leucocyte antigens.

References

1. Raheel S, Shbeeb I, Crowson CA, Matteson EL. Epidemiology of polymyalgia rheumatica 2000-2014 and examination of incidence and survival trends over 45 years: a population-based study. *Arthritis Care Res* 2017; 69: 1282-1285.
2. Cimmino MA, Zaccaria A. Epidemiology of polymyalgia rheumatica. *Clin Exp Rheumatol* 2000; 18: 59-11.
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. Manzo C, Camellino D. Polymyalgia Rheumatica (PMR): Diagnostic and therapeutic issues of an apparently straightforward disease. *Recenti Prog Med* 2017; 108: 221-231.
5. Bird HA, Leeb BF, Montecucco CM, et al. A comparison of the sensitivity of diagnostic criteria for polymyalgia rheumatica. *Ann Rheum Dis* 2005; 64: 626-629.
6. 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: 921-923.
7. Guggino G, Ferrante A, Macaluso F, et al. Pathogenesis of polymyalgia rheumatica. *Reumatismo* 2018; 70: 10-17.
8. McCarty DJ, O’ Duffy JD, Pearson L, et al. Remitting seronegative symmetrical synovitis with pitting edema: RS3PE syndrome. *JAMA* 1985; 254: 2763-2767.
9. Li H, Altman RD, Yao Q. RS3PE: clinical and research development. *Curr Rheumatol Rep* 2015; 17: 49.
10. Cantini F, Salvarani C, Olivieri I, et al. Remitting seronegative symmetrical synovitis with pitting oedema (RS3PE) syndrome: a prospective follow up and magnetic resonance imaging study. *Ann Rheum Dis* 1999; 58: 230-236.
11. Muller S, Hider S, Helliwell T, et al. The real evidence for polymyalgia rheumatica as a paraneoplastic syndrome. *Reumatismo* 2018; 70: 23-34.

12. Manzo C, Natale M. Polymyalgia rheumatica in association with remitting seronegative synovitis with pitting edema: a neoplastic warning. *Can Geriatr J* 2017; 20: 94-96.
13. Emamifar A, Hess S, Gildberg-Mortensen R, Jensen Hansen IM. Association of Remitting Seronegative Symmetrical Synovitis with Pitting Edema, Polymyalgia Rheumatica, and Adenocarcinoma of the Prostate. *Am J Case Rep* 2016; 17: 60-64.
14. Abdel-Wahab N, Shah M, Suarez-Almazor ME. Adverse events associated with immune checkpoint blockade in patients with cancer: a systematic review of case reports. *PLoS One* 2016; 11: e0160221.
15. Belkhir R, Burel SL, Dunogeant L, et al. Rheumatoid arthritis and polymyalgia rheumatica occurring after immune checkpoint inhibitor treatment. *Ann Rheum Dis* 2017; 76: 1747-1750.
16. Gauci ML, Baroudjian B, Laly P, et al. Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome induced by nivolumab. *Semin Arthritis Rheum* 2017; 47: 281-287.
17. Pundole X, Abdel-Wahab N, Suarez-Almazor ME. Arthritis risk with immune checkpoint inhibitor therapy for cancer. *Curr Opin Rheumatol* 2019; 31: 293-299.
18. Healey LA. Long-term follow-up of polymyalgia rheumatica: evidence of synovitis. *Semin Arthritis Rheum* 1984; 13: 322-328.
19. Han RF, Pan JG. Can intravesical bacillus Calmette-Guerin reduce recurrence in patients with superficial bladder cancer? A meta-analysis of randomized trials. *Urology* 2006; 67: 1216-1223.
20. Racioppi M, Di Gianfrancesco L, Ragonese M, et al. The challenges of Bacillus of Calmette-Guerin (BCG) therapy for high risk non muscle invasive bladder cancer treatment in older patients. *J Ger Oncol* 2018; 9: 507-512.
21. Lamm DL, Stogdill VD, Stogdill BJ, Crispin RG. Complications of bacillus Calmette-Guerin immunotherapy in 1,278 patients with bladder cancer. *J Urol* 1986; 135: 272-274.
22. 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: 1150-1159.
23. Mouly S, Berenbaum F, Kaplan G. Remitting seronegative symmetrical synovitis with pitting edema following intravesical bacillus Calmette-Guerin instillation. *J Rheumatol* 2001; 28: 1699-1701.
24. El Mazhou S, Popa L, Constantin A, et al. Remitting seronegative symmetrical synovitis pitting oedema after BCG instillation. *Clin Rheum* 2006; 25: 566-567.
25. 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.
26. Stavris C, Retornaz F, Charpin C, et al. Vasculites des gros vaisseaux induites par une prise medicamenteuse: 2 nouveaux cas secondaires à l'administration de BCG-thérapie et de G-CSF. *Rev Med Int* 2016; 37 (Suppl 2): A179.
27. Manzo C, Natale M. Polymyalgia rheumatica and cancer risk: the importance of the diagnostic set. *Open Access Rheumatol* 2016; 8: 93-95.
28. Dejaco C, Duftner C, Buttgerit F, et al. The spectrum of giant cell arteritis and polymyalgia rheumatica: revisiting the concept of the disease. *Rheumatology (Oxford)* 2017; 56: 506-515.
29. Marzo-Ortega H, McGonagle D, O'Connor P, et al. Subclinical vasculitis in polymyalgia rheumatica. *Ann Rheum Dis* 2001; 60: 1058-1059.
30. Pahari S, Deepyan 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.