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Case report of polymyalgia rheumatica in a male patient with three different neoplasms treated with pembrolizumab

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SUMMARY

In this manuscript we aim to describe a particular case of a 63 years-old man who developed three different malignancies (one was a rare case of breast cancer) among nearly five years. In particular, for the diagnosis of melanoma, he was treated with pembrolizumab, a PD-1 inhibitor.

After few months of treatment with pembrolizumab, the patient reported the onset of musculoskeletal symptoms such as inflammatory pain at the shoulders and morning stiffness, with raised CRP and ESR and imaging evidence of bursitis and tenosynovitis. A polymyalgia-like syndrome was diagnosed. Understanding if these manifestations are linked to the use of pembrolizumab or to a paraneoplastic syndrome, and how to manage the patient, was the real challenge.

Key words: *Pembrolizumab; polymyalgia rheumatica; immune-checkpoint inhibitors.*

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INTRODUCTION

Immune-checkpoint inhibitors have been recently developed as efficacious therapies against different types of cancer, and their use is now rapidly increasing. However, these treatments can lead to an immune activation that triggers symptoms and signs of autoimmune diseases (1). Since the introduction of immune-checkpoint inhibitors, different cases of rheumatic and autoimmune diseases have been reported, although they remain rare and often misdiagnosed for many reasons (2). We report a very rare and particular case of a 63-year-old man with three different malignancies (bowel infiltrating adenocarcinoma, melanoma and breast adenocarcinoma) treated with anti-programmed cell death protein 1 (PD-1) antibody pembrolizumab, who developed a polymyalgia rheumatica (PMR)-like syndrome.

CASE REPORT

In 2014, a 63-year-old man, smoker of 10 cigarettes/day, with a medical history of hypertension and hyperlipidemia was initially evaluated due the presence of occult fecal blood. The patient underwent a pancolonoscopy, which highlighted, at sigmoid level, a sessile neoformation of 4 cm of diameter, covered with fragile, partially eroded and easily bleeding mucosa. Multiple biopsies were performed on the lesion leading to the diagnosis of infiltrating adenocarcinoma. A video-laparoscopic left hemicolectomy with loco-regional lymphadenectomy and colorectal anastomosis was performed at our hospital. The patient received conventional adjuvant chemotherapy and in the follow-up visits he was periodically examined with computed tomography (CT) scans that showed no metastasis.

In 2018, a malignant melanoma in the interscapular region was diagnosed. The patient was re-studied systemically with a total body-contrast enhanced CT examination, which identified 2 suspicious lymphnodes in the right axillary site. These lymphnodes were surgically removed and histologically analyzed, leading to a diagnosis of intra and peri-lymph node metastases of melanoma. Furthermore, the presence of the

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p.Val600Glu mutation (c.1799T>A) was found in the *BRAF* gene on the previously removed skin lesion. The patient underwent adjuvant immunotherapy with Pembrolizumab in December 2018.

In May 2019, the patient reported the loss of serum-blood secretion from the right breast. This secretion was analyzed and showed epithelial elements organized in papillomatous structures, with phenomena of pseudo-cannibalism, strongly suggesting malignancy. MRI showed the presence of ductal ectasia with proteinaceous material and intense enhancement after administration of contrast medium in the retro-areolar area of the right breast. A simple mastectomy was performed and the histological analysis led to the rare diagnosis of ductal carcinoma in situ in a male patient. Therefore, the patient started an adjuvant therapy with tamoxifen 20 mg/day in combination with pembrolizumab. After 2 months, the control chest CT scan showed a nodular opacity of 24 mm in the lingula and hilar adenopathies on the left lung, suspected for metastasis. The patient underwent a total body PET-CT examination with 18-FDG that showed high cellular turn-over lesions in the left lung and homolateral secondary lymphatic lesions, both mediastinal and peri-bronchial. Secondary lesions were also found along the course of the upper mesenteric and hepatic vessels.

After the diagnosis of breast cancer and after few months of treatment for melanoma with pembrolizumab, the patient reported the onset of bilateral muscle pain and stiffness in the shoulders and hips in July 2019. Pain was more severe in the morning and associated with severe stiffness that persisted for hours. Normal daily routine activities seemed to slightly improve joint pain.

A rheumatological evaluation was performed. Physical examination did not reveal the presence of painful or swollen peripheral joints, while tenderness and functional limitation were present in the shoulder and pelvic girdles. Laboratory tests revealed an erythrocyte sedimentation rate (ESR) of 40 mm/h (normal value: 0-22 mm/h) and a C-reactive protein (CRP) of 5 mg/dL (normal value: <1 mg/dL), while rheumatoid factor (RF), anticitrullinated peptide antibodies (ACPA) and anti-nuclear antibodies (ANA) were negative. Ultrasonography of both shoulders demonstrated the presence of bursitis and bilateral tenosynovitis of the caput longus of biceps. Power Doppler was negative (Figure 1). No clinical signs of giant cell arteritis were found. No clinical and ultrasonographic signs of spondyloarthritis were found (3). A diagnosis of PMR-like syndrome was made (the patient met the 2012 provisional classification criteria for PMR) (4).

The patient started oral prednisone 20 mg daily, which was tapered over the next two weeks according to the guidelines of the American Society of Clinical Oncology and according to the oncologist's advice, despite the evidence that steroids may diminish the efficacy of PD-1 inhibitor therapy (5). Within 24 hours, the patient reported a significant improvement in the intensity of pain and proximal muscle weakness. Both ESR and CRP normalized after 4 weeks of treatment. However, a flare was experienced when prednisone was tapered down to 5 mg daily. After 3 months the patient was in treatment with Prednisone 10 mg and found in good clinical condition, but pembrolizumab had been stopped by the oncologist one month before. Partial response of the cancer was maintained after the cessation of pembrolizumab as showed by a new PET-CT, in which a FDG-uptake reduction of pulmonary metastatic lesions was found. However, a high turn-over subcarinal lymphadenopathy was identified (Figure 2). The patient was carefully monitored and the treatment with pembrolizumab was recently re-introduced when

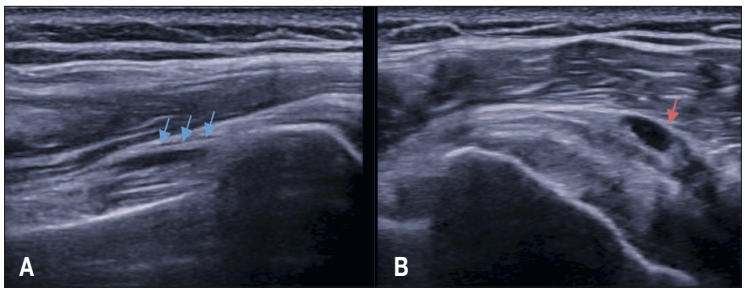

Figure 1 - A) Blue arrows: Tenosynovitis of the right biceps long head tendon (longitudinal view); B) Red arrow: Subacromial bursitis of the left shoulder.

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prednisone was tapered down to 5 mg daily with an acceptable outcome.

DISCUSSION AND CONCLUSIONS

Immune-related adverse events induced by cancer immunotherapy have been described in a variety of clinical settings. Rheumatic and musculoskeletal diseases were reported less often in clinical trials, while most cases originate from case reports or case series (2, 6, 7). Our patient experienced severe symptoms of PMR, which compromised his quality of life. Interestingly, the treatment with pembrolizumab triggered his symptoms a few months after it was started. In a recent report, Capelli and colleagues reviewed the published literature on rheumatic diseases triggered by immune-check points inhibitors. Arthritis was reported in 5/33 clinical trials, and vasculitis was reported in 2 only. Case reports showed the occurrence of inflammatory arthritis, vasculitis, myositis, and lupus nephritis (6), and two more cases of delayed onset inflammatory polyarthritis after a treatment with pembrolizumab for metastatic melanoma were reported.

In a recent systematic review and meta-analysis of studies performed on cancer patients receiving anti-PD-1 and anti-PDL1 agents, only few individual cases of arthritis were reported at a rate below 1%. However, across the groups, musculoskeletal complaints were very common, ranging from 9 to 18% for arthralgia, 2 to 16% for back pain, 4 to 6% for musculoskeletal pain, and 4 to 16% for myalgia, suggesting that organ specific immune adverse events are uncommon with anti-PD-1 drugs, yet they are associated with a higher risk compared to control treatments (8, 9).

The pathophysiology of pembrolizumab-induced inflammatory arthritis has not yet been clarified. It has been suggested that anti-PD-1 antibodies may enhance autoimmunity by activating T cell function or may allow previously dormant arthritogenic clones to expand, as suggested by Chan et al. who also reported a case of tenosynovitis and arthritis in a patient with melanoma treated with pembrolizumab (10).

Our case is unique, because the patient experienced three different neoplasms, one of these being a rare case of breast cancer in a male. However, if the onset of PMR was triggered by pembrolizumab or the presence of neoplasms itself is the object of the discussion.

Studies suggest that up to 8% of patients with cancer may have a paraneoplastic syndrome (9) that can include paraneoplastic polyarthritis and relapsing seronegative symmetric synovitis with pitting edema (RS3PE) (11). Considering that no specific diagnostic test is available for a condition such as PMR, in our patient it was difficult to establish whether there was a true association between PMR and malignancies, or it was an incidental co-existence of the two conditions, or it was induced by pembrolizumab. The onset of PMR shortly after the diagnosis of breast cancer may indicate a paraneoplastic syndrome and there are reports of PMR-like symptoms in patients with ductal carcinoma (12). Moreover, according to the Naranjo scale (13), our patient scored less than 4, indicating that pembrolizumab only *possibly* caused PMR. However, the good response during the period of follow-up without pembrolizumab and the presence of a flare when prednisone was tapered may suggest a delayed

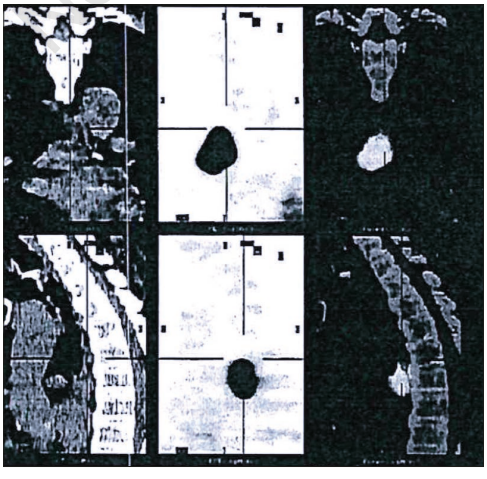

Figure 2 - Positron emission tomography-computed tomographic scan showing high turn-over subcarinal lymphadenopathy.

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immune-related side effect of the treatment with pembrolizumab. Finally, the presence of three neoplasms and a treatment with an immune-check point inhibitor may suggest that drug-induced or cancer-induced alterations in immune response (such as expansion of CD8+ lymphocytes or other immune cells) might have occurred (14).
In conclusion, the management of patient with these manifestations is particularly complex and must take into account several aspects: in particular, the need to control the progression of cancer and musculoskeletal symptoms, which can be particularly invalidating and have a significant impact on his quality of life.

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Contributions
All authors made substantial contributions to all of these sections: conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article, revising it critically for important intellectual content and final approval of the version to be submitted. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Conflict of interests
The authors declare no potential conflict of interests.

Ethics approval and consent to participate
Patient's informed consent to use personal data was obtained and attached with files.

REFERENCES

1. Ibraheim H, Perucha E, Powell N. et al. Pathology of immune-mediated tissue lesions following treatment with immune checkpoint inhibitors. Rheumatology (Oxford). 2019; 1: vii17-vii28.
2. Benfaremo D, Manfredi L, Luchetti MM, et al. Musculoskeletal and rheumatic diseases induced by immune checkpoint inhibitors: a review of the literature. Curr Drug Saf. 2018; 13: 150-64.
3. Perrotta FM, Astorri D, Zappia M, et al. An ultrasonographic study of enthesis in early psoriatic arthritis patients naive to traditional and biologic DMARDs treatment. Rheumatol Int. 2016; 36: 1579-83.
4. Dasgupta B, Cimmino MA, Maradit-Kremers H, et al. 2012 provisional classification criteria for polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative. Ann Rheum Dis. 2012; 71: 484-92.
5. Brahmer JR, Lacchetti C, Schneider BJ, et al. National Comprehensive Cancer Network. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2018; 36: 1714-68.
6. Cappelli LC, Gutierrez AK, Bingham CO III, et al. Rheumatic and musculoskeletal immune-related adverse events due to immune checkpoint inhibitors: a systematic review of the literature. Arthritis Care Res. 2016; 69: 1751-63.
7. Cappelli LC, Shah AA, Bingham CO III. Immune-related adverse effects of cancer immunotherapy-implications for rheumatology. Rheum Dis Clin North Am. 2017; 43: 65-78.
8. Spathas N, Economopoulou P, Cheila M, et al. Inflammatory arthritis induced by pembrolizumab in a patient with head and neck squamous cell carcinoma. Front Oncol 2018; 8: 409.
9. Baxi S, Yang A, Gennarelli RL, et al. Immune-related adverse events for anti-PD-1 and anti-PD-L1 drugs: systematic review and meta-analysis. BMJ 2018; 360: k793.
10. Chan MM, Kefford RF, Carlino M, et al. Arthritis and tenosynovitis associated with the anti-PD1 antibody pembrolizumab in metastatic melanoma. J Immunother. 2015; 38: 37-9.
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. Keith MP, Gilliland WR. Polymyalgia rheumatica and breast cancer. J Clin Rheumatol. 2006; 12: 199-200.
13. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reaction. Clin Pharmacol Ther. 1981; 30: 239-45.
14. Guggino G, Ferrante A, Macaluso F, et al. Pathogenesis of polymyalgia rheumatica. Reumatismo. 2018; 70: 10-7.

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