Rheumatic immune-related adverse events from checkpoint inhibitor therapy: a case series

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Abstract

Immune checkpoint inhibitors (ICIs) targeting cytotoxic T-lymphocyte associated protein-4 (CTLA-4), programmed cell death protein-1 (PD-1), and its ligand PD-L1 are established cancer immunotherapies for solid tumor and hematologic malignancies. These therapies are involved in immune-related adverse events (irAE), both general and rheumatic ones. In general, immune-related adverse events (irAE) management includes drug-holding, tapering doses of corticosteroids, and specific immunosuppression for clinically severe cases, such as infliximab or mycophenolate.

Introduction

Immune checkpoint inhibitors (ICIs) targeting cytotoxic T-lymphocyte associated protein-4 (CTLA-4), programmed cell death protein-1 (PD-1), and its ligand PD-L1 are established cancer immunotherapies for solid tumor and hematologic malignancies.[1,2]

It is well known that tumor cells are able to evade endogenous immune responses by activating inhibitory receptors on tumor-specific T cells to downregulate and suppress T-cell function.[3,4] Checkpoint inhibitors counteract CLTA-4, PD-1 and PD-L1, three distinct proteins that regulate T-cell activity.[3,5] CLTA-4 and PD-1 are receptors that reside directly on the T-cell membrane. When these receptors are blocked, or inhibited, the T cell becomes activated.[3,5] Instead, PD-L1 resides on the cancer cell. When this is blocked, the cancer cell can no longer downregulate or evade T cells, thus the immune activity is stimulated.[3,6] In particular, on the surface of the T cells there are CTLA-4 and CD28, which are the inhibitor and the stimulator receptor respectively, inducing downregulation of T cells to protect the body from autoimmunity or trigger T-cell activation, respectively.[5,7] Under normal physiologic circumstances, the ligands B7-1 and B7-2, expressed by antigen-presenting cells (APC), bind to CD28 on T cells to stimulate activation of the immune response; then T cells express CTLA-4, which has a higher affinity for B7-1 and B7-2; so B7 ligands bind to CTLA-4 rather than CD28, the stimulatory effect is overcome and the T cell is deactivated. This is a system of self-regulation, that allows for appropriate activation of T cells to attack foreign antigens and prevent chronic autoimmune processes.[3-8] Like CTLA-4, PD-1 downregulates immune cell activity when bound by the ligand PD-L1.[5] At present, ipilimumab, nivolumab, pembrolizumab, and the ipilimumab/nivolumab combination are U.S. Food and Drug Administration approved for metastatic melanoma;[1,9,10] nivolumab, pembrolizumab, and atezolizumab monotherapy for non-small cell lung cancer (NSCLC);[11,12] nivolumab monotherapy for renal cell carcinoma (RCC), head and neck squamous carcinoma, and Hodgkin's lymphoma;[13-15] pembrolizumab for head and neck squamous carcinoma[16] and atezolizumab for urothelial carcinoma.[17] In general, anti-PD-1/PD-L1 monotherapy is associated with a relatively mild toxicity profile.[18] However, immune-related adverse events (irAEs) may develop and lead to disabling symptoms that can be challenging to diagnose and manage.[19] Immune-related adverse events (irAEs) can be general and rheumatic adverse events. Rheumatic adverse events include inflammatory arthritis (IA), arthralgia, tenosynovitis, non-erosive Jaccoud's arthropathy and psoriatic arthritis and polymyalgia rheumatic-like syndrome.[20-22] Inflammatory arthritis (IA) has an estimated incidence of 1%-7%, while arthralgias have an estimated incidence of 4% to 22%.[23,24] In the largest series of ICI-related IA published by Johns Hopkins investigators, three distinct clinical phenotypes of the clinical Inflammatory arthritis presentation in these patients are described: i) rheumatoid arthritis (RA); ii) reactive arthritis; and iii) seronegative spondyloarthritis.[25] Patients affected by rheumatoid arthritis related to ICI tended to require higher corticosteroid doses (1-2 mg/kg/day prednisone/equivalent), when compared with patients with de novo RA (usually no more than 10-20 mg/day), and had symptoms which persisted following ICI discontinuation.[25] Patients with reactive-arthritis-like IA had arthritis, conjunctivitis, and urethritis and were

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treated with anti-TNF inhibitors. Imaging in these cases (musculoskeletal ultrasound [US], musculoskeletal magnetic resonance imaging [MRI]) demonstrated joint effusions, synovial proliferation, and increased vascularity, with bony erosions shortly after the onset of symptoms in these patients. Synovial fluid analysis completed in a subset of patients demonstrated an inflammatory picture with high polymorphonuclear cells (polymorphonuclear leukocytes [PMNS]: 70%, white blood cell count [WBC] range: 9854-28,400 cells/mm^3). Autoantibody assessments were performed, but none was positive for rheumatoid factor and anti-cyclic citrullinated peptide antibodies.[25] In literature a proposed algorithm is described for the diagnostic workup and management of inflammatory arthritis that can occur with immune checkpoint blockade, stratified by grade of common toxicity criteria for adverse events.

Rheumatologists classify patients according to severity and duration of symptoms (grade 2+, lasting >4 weeks), imaging, and steroid dose (requirement of >20 mg of prednisone per day that cannot be tapered to <10 mg within 4 weeks). In patients with one joint disproportionately affected or resistant to treatment, metastatic disease should be considered. To treat ICI-related IA, nonsteroidal anti-inflammatory drugs (NSAIDs) can be used for supportive management. Intra-articular steroids can be used as local therapy for those with limited involvement of accessible joints, when less than three joints are affected. Grade 1 cases should be managed supportively using NSAIDs, and ICIs may be continued with close monitoring for moderate and persistent symptoms that require intervention (grade 2). Grade 2 cases should be managed supportively using prednisone 20 mg daily for 4-6 weeks, increasing to 1 mg/kg/day or equivalent if there is no response in 4-6 weeks and escalate to grade 3 management. In these cases, it is necessary to consider holding immunotherapy.

In grade 3 cases, additional immunosuppression used successfully included: conventional DMARDs and biologic DMARD or small molecules. Methotrexate, sulfasalazine, and leflunomide can be considered for use as steroid-sparing agents for IA. The choice of biologic DMARD should also be considered depending on the presence of other immune-related adverse events (irAEs). So, antiTNF alfa monoclonal antibodies (*e.g.*, infliximab, adalimumab) may be preferable to soluble receptors (etanercept) in patients with immune-related colitis, while antiIL6 Inhibitors such as tocilizumab and tofacitinib should probably be avoided due to possible potentiation of gastrointestinal perforation.[27,28] In addition, abatacept, which increases T-cell activation through CD28, may need to be avoided lest it abrogates the effect of anti-CTLA-4 ICIs.[29] This algorithm will require validation in larger datasets in the future. A critical and presently unanswered question is what proportion of these rheumatic irAEs represent the occurrence of classic rheumatic diseases or, alternatively, represent new clinical variants with potentially different pathogenesis, clinical course and treatment responsiveness.[30]

Case Reports

Case 1

The first case is about a 75-year-old woman.

In anamnesis: familiarity for gastric and breast cancer. Nonsmoker. Insulin dependent type II diabetes mellitus and high blood pressure. In February 2008 hospitalization for right radical nephrectomy and cavotomy with removal of neoplastic thrombus and locoregional lymphadenectomy for a histologically proven neoplasm renal cell carcinoma clear cell variant with nucleolar grade 2 if Fuhrman, infiltrating the adipose tissue of the renal sinus and with neoplastic thrombosis massive renal vein to the hilum. Various therapeutic lines were started: Sutinib, Everolimus, Sorafenib, Gemgitabine + oxaliplatin, some suspended due to toxicity of different types and others due to disease progression. In February 2016 there was a total body disease progression in CT scan (especially in the lung); therefore, fifth line with nivolumab iv was started every 2 weeks with partial radiological response. Subsequent appearance of polyarthralgia with morning stiffness >1 hour in conjunction with the start of the new immunotherapy: therefore, she came to our observation. Rheumatological evaluation was requested by the oncologist for suspicion of autoimmune arthritis triggered by immunological treatment. She denied any familiarity with rheumatic diseases or psoriasis. The rheumatological physical examination showed minimal swelling of the wrists, swelling of the knees and pain during mobilization of the shoulders. Laboratory tests showed ESR 86 mm/1 h; PCR 17.76 mg/dL, low-titre positive FR 23 IU/mL; ANA and anti-CCP were negative. Normal blood count and liver-kidney function. Knee X-rays excluded chondrocalcinosis. RX hands and feet showed an osteoarthritis picture, without erosion. Musculotendinous ultrasounds of the shoulders documented bilateral TCLB tenovaginalitis, bilateral positive PwD radiocarpic synovitis on the wrists and abundant effusion in the supra-patellar recess on both sides of the knees. Diagnosis of seropositive FR and negative anti-CCP arthritis with polymyalgic commitment (unclear) in the patient on immunological therapy for renal cell carcinoma, clear cell variant with lung metastases. In agreement with the oncologist, the steroid cycle was set at low doses (<15 mg prednisone/day) to avoid suppressing the efficacy of immunotherapy with nivolumab (considering the partial response and the various chemotherapy lines already administered) with clinical benefits.

Case 2

The second case is about a 64-year-old man. In anamnesis: diabetes mellitus on oral therapy, high blood pressure. History of lung neoformation (G3 Spinocellular Carcinoma) first treated with cisplatin and gemcitabine; subsequently, for disease progression, therapy with Nivolumab 240 mg every 2 weeks iv. About 4 months after starting nivolumab, arthralgias appeared and also swelling of the right hand. The rheumatological physical examination showed pain during mobilization of wrist and small joints in the right hand; no impotence to the tracks; free from peripheral synovitis. Right hand radiography documented diffuse osteoporosis and osteoarthrosis of articulation of the hands and some geodesic areola in the carpal skeletal segments. Blood tests showed ESR 77 and PCR 33 mg/L (<10), negative rheumatoid factor and anti-CCP. Normal liver and kidney function. Normal uricemia. Arthralgias were diagnosed during immunotherapy with nivolumab. Indicated therapy with low-dose steroid (Prednisone 10 mg/day slowly reducible to 5 mg/day) with strict control of glycemic values.

Case 3

The third case is about a 58-year-old man, metal worker. Nothing significant in medical history except for skin psoriasis for several years. No personal or family history of autoimmune or rheumatological diseases. In 2015 diagnosis of metastatic occult melanoma BRAF WILD TYPE M1a (pTxN1b). Treated with right axillary lymphadenectomy. In 2016 there was documented restarting of lung cancer disease: indication for the start of immunotherapy with checkpoint inhibitors, therefore, in April 2017, the patient started immunotherapy with PEMBROLIZUMAB 174 mg for 11 cycles every 3 weeks. The response to immunotherapy was excellent: already from the PET check in June 2017, the hypercaptation areas previ-

ously reported was no longer visible. In June 2018, the patient reported the appearance of generalized asthenia and malaise, polyarthromyalgia, stiffness of the scapular and pelvic girdles, more intense at awakening, and bilateral imprinted edema of the handsand, to a lesser extent, of the feet. Laboratory tests showed: negative inflammation indices, negative FR and ACPA, negative autoimmunity (ANA, ENA, ANCA). We concluded for polymyalgia-like syndrome (RS3PE variant). Attempted therapeutic cycle with NSAIDs, completely ineffective, started steroid therapy with prednisone 12.5 mg/day with immediate benefit both on the joint and on the muscle component. However, when the steroid was reduced below 10 mg/day, the girdle deficit and modest symmetrical edema of the hands reappeared. It was therefore decided to introduce immunosuppressive therapy with hydroxychloroquine 200mg/day, in an attempt to reduce the steroid to the minimum effective dose, therefore MTX 15mg/week, always with good clinical response.

Discussion

Immune checkpoint inhibitors (ICIs) are new cancer immunotherapies for solid tumor and hematologic malignancies and it's well known that they can give immune-related adverse events (irAEs) and in particular rheumatic ones.[1,2] Today, there is a proposed algorithm for the diagnostic workup and management of inflammatory arthritis that can occur with immune checkpoint blockade, stratified by Common Toxicity Criteria for Adverse Events grade.[26]

Up to date there are insufficient data to distinguish if these cases of irAE-PMR are equal to the idiopathic form of the disease or rather a new nosological entity. A relevant clinical fact is that 37% of cases of ICI-induced PMR require more aggressive therapy with steroids than is traditionally used to treat classic PMR probably due to a different pathogenesis. Moreover, it was noted that inflammation may persist, even after cessation of checkpoint inhibitor therapy; so, this data could explain the need for prolonged steroid use.[31-33] Immune-related adverse events (irAE) management includes discontinuation of the drug ICI, downshift cycle of steroid and sometimes the use of specific immunosuppression for clinically severe cases.

Conclusions

Checkpoint inhibitor therapy has led to a paradigm shift in the field of oncology, as it achieves significant survival benefits in patients with an ever-growing list of malignancies. Their use, however, is associated with a spectrum of immune-related adverse events (irAEs), both general and rheumatic, which threaten their overall effectiveness. Therefore, it's important to recognize immune-related adverse events and treat them in collaboration with oncologists.

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