Published in final edited form as:

Clin Genitourin Cancer. 2019 June ; 17(3): e549–e552. doi:10.1016/j.clgc.2019.02.005.

A Case of Anti—PD-L1-associated Remitting Seronegative Symmetric Synovitis With Pitting Edema

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Keywords

Cancer immunotherapy; Checkpoint inhibitor toxicity; Immune-related adverse event; Immune-mediated arthritis; mCRPC

Introduction

Utilization of immune checkpoint inhibitor monoclonal antibodies has become the standard of care for several malignancies in recent years, with United States Food and Drug Administration (FDA) approvals for a variety of indications.[1–15] The targets of FDA-approved checkpoint inhibitors are programmed cell death protein-1 (PD-1) (nivolumab, pembrolizumab), programmed death-ligand 1 (PD-L1) (avelumab, atezolizumab, durvalumab), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) (ipilimu-mab). Blockade of these inhibitory molecules in tumor tissue or on immune cells in peripheral immune organs can lead to anti-tumor activity.[16]

AntiePD-1 monoclonal antibody activity has been observed in subsets of patients with metastatic castration-resistant prostate cancer (mCRPC) progressing on the androgen receptor antagonist enzalutamide (an androgen receptor antagonist approved for mCRPC) with the combination of pembrolizumab and continued enzalutamide (20% with a prostate-specific antigen reduction ≥ 50%).[15,17] However, current evidence does not favor a role for checkpoint inhibitor monotherapy in unselected patients with mCRPC because antiePD-1/PD-L1 agents have demonstrated limited activity in early phase trials,[18–20] and 2 phase III trials using ipilimumab were negative for a survival advantage.[21,22]

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Disclosure

The authors have stated that they have no conflicts of interest.

Although single-agent use of checkpoint inhibitors appears to be less promising, combination trials are ongoing in multiple clinical settings for prostate cancer. The poly (ADP-ribose) polymerase (PARP) inhibitor, olaparib, is active in prostate cancers harboring DNA damage repair gene (eg, *BRCA1*, *BRCA2*, and *ATM*) muta-tions.[23] Olaparib received FDA breakthrough designation for this indication. The drug is also approved for *BRCA* mutant human epidermal growth factor receptor 2-negative breast cancer (Olym-piAD trial)[24] and as maintenance therapy for women with *BRCA* mutant[25] and now all women[26] with advanced ovarian cancer.

Olaparib is currently under investigation in combination with durvalumab in an unselected population of patients with mCRPC (NCT02484404). Preliminary data showed a prostate-specific antigen decline of > 30% or radiographic response in 9 of 17 patients with prostate cancer.[27] Ongoing correlative studies are investigating potential mechanisms of action of the combination.

In addition to facilitating immune-mediated tumor destruction, checkpoint inhibitors can impair peripheral immune tolerance,[28] resulting in inflammatory immune-related adverse events (irAEs) largely attributed to T cell-mediated damage to normal tissue.[2] The American Society of Clinical Oncology recently published guidelines for management of these toxicities.[29] Depending on grade, irAE management may involve holding drug and initiating corticosteroids, or disease-modifying anti-rheumatologic drugs. These clinical entities were first observed in patients treated with the anti-CTLA monoclonal antibody, ipilimumab.[30] However, treatment with antiePD-1/PD-L1 monoclonal antibodies can also cause irAEs, including hepatitis,[18] skin disorders,[31,32] pneumonitis,[31] tenosynovitis,[33] and enteropathies.[34]

A variety of immune checkpoint inhibitor-related inflammatory joint disorders have been observed and are summarized elsewhere.[35] Serologies from limited experiences with these arthritides are typically rheumatoid factor-negative, and patients often require steroid doses exceeding prednisone 1 to 2 mg/kg/day (or equivalent),[32,36,37] although some have reported success with steroid-sparing regimens.[33,36]

Remitting seronegative, symmetric synovitis with pitting edema (RS3PE) is a rheumatoid factor-negative, sudden-onset polyarthritis syndrome typically observed in the elderly and characterized by concomitant pitting edema of the dorsal hands and feet. Association of RS3PE with malignancy[38] and rheumatologic disease has been noted, and elevated levels of serum vascular endothelial growth factor, compared with healthy volunteer controls, have been observed in patients with RS3PE.[39] One report describes elevated levels of serum matrix metalloproteinase-3 that normalized after successful treatment of RS3PE with corticosteroids.[40] Nonetheless, a complete understanding of the underlying pathology is currently lacking, and, to our knowledge, no studies of tissue samples are available to implicate a specific immune pathway responsible for this pathologic entity.[41]

Four cases of an anti-PD-1 antibody-associated RS3PE have been reported in patients receiving nivolumab, 3 for advanced melanoma and 1 for nonesmall-cell lung cancer.[35,42–44]

Here, we present a case of RS3PE in a man with mCRPC receiving durvalumab and olaparib.

Case Presentation

A 70-year-old man with mCRPC was initially diagnosed with T3bN0M0, Gleason score 3 + 5 = 8 disease at 56 years of age. The patient initially underwent radical prostatectomy. Subsequent treatments included whole tumor vaccine (clinical trial) and salvage radiation therapy. Once the patient became castration-resistant, he was treated with bicalutamide in addition to androgen deprivation, palliative radiation therapy, enzalutamide plus a vector-based vaccine (clinical trial), and radium-223 plus abiraterone acetate. After progression on abiraterone acetate, the patient began treatment on a clinical trial (NCT02734004) combining the anti-PD-L1 monoclonal antibody, durvalumab (1500 mg intravenously once every 28-day cycle) plus the PARP inhibitor, olaparib (300 mg tablets orally twice daily).

One week following initiation of treatment, the patient developed bilateral pain (intensity 2–3/10) and mild swelling of the hands and wrists. These symptoms did not impair activities of daily living and were relieved with non-steroidal anti-inflammatory drugs (NSAIDs). Mild diffuse non-pitting edema of the hands was observed bilaterally. These symptoms gradually worsened and were no longer relieved by NSAIDs. Olaparib was held starting cycle 2, week 2; however, the pain and swelling worsened and began to impair function, strength, and range of motion of the wrists and hands. Activities such as eating and dressing required increased effort. The patient returned to clinic for evaluation on cycle 3, day 1. The diffuse non-pitting edema of the hands, previously observed, increased bilaterally. Additionally, synovitis of the proximal interphalangeal (PIP) and bilateral third metacarpophalangeal joints was present, as well as tenderness, warmth, and swelling of the wrists bilaterally. He exhibited mild limitation in the ability to make a complete fist bilaterally. The remainder of the musculoskeletal exam was unremarkable. In addition to a rheumatology consultation, durvalumab was discontinued, and corticosteroid treatment (prednisone 15 mg orally) was initiated. Testing for rheumatoid factor and anti-nuclear antibodies were negative. C-reactive protein was within normal limits. A diagnosis of RS3PE was made. He noted improvement of arthralgia within 24 hours of starting prednisone. Olaparib was resumed.

Nine days after completing the prednisone taper, pain and swelling of the fingers and PIP joints recurred, in addition to new pain and edema in the distal interphalangeal joints. The pain was mild and controlled with NSAIDs. These symptoms did not interfere with function. Six weeks following cessation of prednisone, the patient developed worsening bilateral PIP, distal interphalangeal, and wrist swelling, which prevented him from bending his fingers. Rheumatoid factor and anti-nuclear antibody testing at that time were again negative. Extended rheumatologic workup for antitopoisomerase 1, anti-centromere, anti-cyclic citrullinated peptide, and anti-parvovirus IgM antibodies was also performed and was negative. Steroid therapy was resumed at a dose of prednisone 60 mg daily. Two days later, the patient reported complete resolution of the pain and swelling. At an office visit 1 week later, no joint swelling was observed. Dosing at 60 mg daily was continued for 5 days and then tapered slowly over 4 weeks. At follow-up 1 month later, he had no joint complaints,

and physical exam of the joints was unremarkable. Imaging demonstrated progression of pleural-based metastases, and the patient was taken off of protocol treatment.

Discussion

Combination immunotherapy, including anti-PD-1/PD-L1 checkpoint inhibitor antibodies, is a dominant strategy under clinical investigation for malignancies, including prostate cancer and other genitourinary malignancies. Joint complaints can occur in patients receiving these agents. Familiarity with this potential irAE is critical for oncologists both in the private and academic settings.

In a meta-analysis of RS3PE, the authors found that patients with successfully treated malignancy-associated RS3PE required, on average, approximately 18.2 mg of prednisone daily.[41] Hence, the patient described here was initially treated with 0.2 mg/kg (15 mg) daily of prednisone. A temporary abatement of symptoms followed; however, symptoms recurred. Upon relapse, 0.8 mg/kg/day of prednisone were prescribed and promptly lead to symptom resolution.

American Society of Clinical Oncology guidelines[29] for management of immune-related inflammatory arthritis includes rheumatologic history including screening for joint stiffness, tenderness, morning accentuation of stiffness and pain, limited range of motion, and improvement of joint symptoms with movement or heat. Workup should include erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, anti-cyclic citrullinated peptide, and anti-parvovirus IgM antibodies, as well as joint imaging when erosion is suspected. Management may be guided based upon the National Institutes of Health Common Toxicity Criteria for Adverse Events grading system. Mild symptoms of pain and joint swelling (grade 1) may be monitored and treated with NSAIDs, or low-dose prednisone bursts, while continuing checkpoint inhibitor. In cases of grade 2 or higher events, which limit activities of daily living, immunotherapy should be held and corticosteroids (10–20 mg prednisone daily) should be initiated. If the joint-related symptoms resolve with corticosteroids, they may be tapered over 4 to 6 weeks. Rheumatology consultation can be helpful for guidance regarding need for imaging to assess joint damage. Cases with severe symptoms (grade 3–4) should be treated with 0.5 to 1 mg/kg/ day of prednisone tapered over 4 to 8 weeks. Corticosteroid-refractory irAEs (no response after 4 weeks of corticosteroids) may require disease-modifying anti-rheumatic drug treatment. Checkpoint inhibitor discontinuation should be permanent in grade 3/4 cases of arthritis.

After initial control, and then failure of low-dose corticosteroids, response to higher dose steroids was prompt and effective. This suggests that a trial of lower dose steroids, aimed at sparing patients the side effects of higher corticosteroid doses, can be a reasonable approach to initial management of immune-related joint complaints. Indeed, Ngo et al report complete resolution of RS3PE with low-dose (0.5 mg/kg) prednisone and uninterrupted nivolumab dosing. Other published reports describe resuming checkpoint inhibitor, following RS3PE symptom resolution, without recurrence of RS3PE.[35,44] This type of management requires adequate follow-up and patient vigilance to ensure timely initiation of steroids upon worsening of symptoms.

Although the response to corticosteroids in the RS3PE case described here favors an immune-mediated etiology, it is unclear if this was related to anti-PD-L1 treatment alone, or additive effects of anti-PD-L1 and PARP inhibitor treatment. Absent local tissue analyses from patients with RS3PE, this pathology remains poorly characterized, and the specific immune mechanisms behind this inflammation are unclear. In a condition that typically resolves with short-term corticosteroid treatment, invasive biopsies are unlikely to guide management and are therefore unlikely to be performed and provide insight into RS3PE mechanisms. However, as clinical trials using checkpoint inhibitors plus other agents become increasingly common, reporting irAE cases will be the dominant means of monitoring incidence and optimizing management (eg, determining if checkpoint inhibitor therapy can safely be continued during or following successful RS3PE treatment with corticosteroids).

Acknowledgments

The authors wish to thank all the patients who participated in this study and their families. The authors wish to thank Ms. Bonnie Casey for editorial assistance. Durvalumab and olaparib were provided through a Cooperative Research and Development Agreement between the National Cancer Institute and AstraZeneca. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

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Clinical Practice Points

- Checkpoint inhibitor monoclonal antibodies have shown minimal activity as monotherapy in advanced prostate cancer; however, their use in combination with other agents is an active area of investigation.
- Checkpoint inhibitors can cause immune-related adverse events, including arthritis, that require cessation of checkpoint inhibitor and high-dose steroids or other immune suppression.
- We report a case of remitting seronegative, symmetric synovitis with pitting edema requiring steroid treatment in a patient with metastatic castrate-resistant prostate cancer receiving durvalumab (anti—programmed death-ligand 1 immune checkpoint blocking antibody) and olaparib (poly [ADP ribose] polymerase inhibitor).
- With an enlarging population of patients with genitourinary malignancies receiving anti-programmed cell death protein-1/programmed death-ligand 1 monoclonal antibodies on trials or as standard treatment, immune-related adverse events are an important clinical entity to include in the differential diagnosis for joint complaints in this population.