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CASE AND RESEARCH LETTER

Anti-PD-1 Induced Musculoskeletal Side Effects Successfully Treated With Hydroxychloroquine in Patients With Advanced Cutaneous Squamous Cell Carcinoma

Tratamiento con hidroxicloroquina de efectos secundarios musculoesqueléticos inducidos por anti-PD-1 en pacientes con carcinoma cutáneo de células escamosas avanzado

To the Editor,

Immunotherapy has become an important therapy in the management of advanced skin cancer. Monotherapy with anti-programmed cell death protein 1 (anti-PD-1) is currently the first-line therapy for advanced cutaneous squamous cell carcinoma (cSCC) in patients ineligible for curative surgery and/or radiotherapy. Cemiplimab has shown an objective response rate of 47.5% with a response duration of more than 6 months in 57% of responding patients.[1] Immune checkpoint inhibitors (ICI) modify the tumor immune microenvironment leading not only to anti-tumor responses but also immune-related adverse effects (irAEs).[2,3] Rheumatic irAEs have been reported in approximately 10% of patients on ICI and there are currently no established guidelines for their therapeutic management, except for recommendations that include avoiding doses >10 mg/day of prednisone or equivalent.[4,5]

We present three cases of advanced cSCC ON anti-PD-1 that presented arthralgia and/or myalgia which were successfully treated with hydroxychloroquine.

- Case #1: An 83-year-old woman with cSCC in the right cheek and unresectable lymph node metastasis refractory to radiation therapy received pembrolizumab 2 mg/kg every 3 weeks. The patient achieved complete clinical and radiological response after 6 cycles and maintained this response after 17 cycles. However, on dose #3, she presented with grade 2 arthromyalgia. Lab test results revealed a C-reactive protein (CRP) level of 33.5 U/L (0–5 mg/L), an erythrocyte sedimentation rate (ESR) of 21 mm/h (1–20 mm/h), and creatin-kinase (CK) levels of 41 U/L (29–168 U/L). At the onset of symptoms, she was prescribed 10 mg/day of prednisone and oral hydroxychloroquine 200 mg/12 h which led to complete symptom relief within 3 weeks (Table 1). Then, a maintenance treatment of 5 mg/day of prednisone and hydroxychloroquine 200 mg/12 h was employed.
- Case #2: An 82-year-old man with recurrent cSCC affecting the right inner canthus, who was ineligible for surgery or radiotherapy on pembrolizumab 2 mg/kg every 3 weeks. He presented clinical and radiological response on cycle #5, which was maintained after 11 cycles. However, on cycle #3, he developed grade 2 arthromyalgia. Lab test results showed a CFP level of 60.5 mg/L (0–5 mg/L), an ESR of 32 mm/h (1–20 mm/h) and CK levels within the normal range. Symptoms resolved with a 1-month initial regimen of prednisone 10 mg/day and oral hydroxychloroquine 200 mg/day (Table 1), after which the treatment was down-titrated to 5 mg/day of prednisone and hydroxychloroquine 200 mg/day as maintenance therapy.
- Case #3: An 80-year-old man with locally advanced recurrent cSCC on his right wrist, refractory to radiotherapy on a 2-year regimen of cemiplimab 350 mg every 3 weeks achieved sustained complete clinical response after treatment discontinuation. On cycle, he presented with grade 2 arthralgia. Blood test results revealed CRP levels of 9.5 mg/L (0–5 mg/L), an ESR of 46 mm/h (1–20 mm/h) and normal CK levels. He was successfully treated with hydroxychloroquine 200 mg twice-daily (Table 1).

In all three cases, the rheumatoid factor and citrullinated peptide antibody tests were negative.

Through these three cases we aim to highlight the effectiveness of hydroxychloroquine in the management of musculoskeletal side effects or rheumatic irAEs. As far as we know, this is the first study ever conducted to show complete resolution using hydroxychloroquine.

Hydroxychloroquine is used in the management of various rheumatological, immunological and infectious diseases. In addition to its well-known anti-inflammatory, immunomodulatory, anti-infective, anti-thrombotic and metabolic effects[6] it also exhibits potent antiproliferative and antimutagenic properties.[7] Furthermore, it is usually considered a safe treatment with few adverse effects. Retinopathy, although concerning, is rare when administered at doses <5 mg/kg/day[7] and is potentially reversible.

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Table 1 Demographic features, cancer types, immunotherapy and rheumatic immune-related adverse events (irAEs).

Patient	Age	Tumor	Differentiation	Immune infiltrate	IHQ – PDL1	Treatment	Response	iRAEs	Weeks until iRAEs	CK level	iRAEs initial treatment	iRAEs maintenance treatment	Improvement
Case #1	83	cSCC – metastatic lymph node	Moderately differentiated	Moderate	30%	Pembrolizumab 2 mg/kg/3 weeks	CR	Arthralgia and myalgia	6	Normal	HCQ 200 mg/12 h Prednisone 10 mg/day 4 weeks	HCQ 200 mg/12 h Prednisone 5 mg/day	Significant
Case #2	82	Unresectable cSCC	Moderately differentiated	Moderate	40%	Pembrolizumab 2 mg/kg/3 weeks	CR	Arthralgia and myalgia	6	Normal	HCQ 200 mg/day Prednisone 10 mg/day 3 weeks	HCQ 200 mg/day Prednisone 5 mg/day	Significant
Case #3	80	Unresectable cSCC	Well differentiated	Poor	<1%	Cemiplimab 350 mg/3 weeks	CR	Arthralgia	3	Normal	HCQ 200 mg/day	HCQ 200 mg/day	Significant

F: female; M: male; CR: complete response; IHQ: immunohistochemistry; CK: creatine kinase; HCQ: hydroxychloroquine.

The actual prevalence of rheumatic irAEs is estimated to be around 10% but there are limited studies reporting prevalence of this disease, likely due to their relatively mild nature and sometimes lacking clinical suspicion.[4,8] The most common rheumatic irAEs include arthralgia, myalgia, arthritis and polymyalgia rheumatic-like syndrome.[5] Some studies indicate that the prevalence of arthralgia ranges from 1% up to 43% vs 1% up to 7% of arthritis.[5] These side effects are more commonly associate with anti-PD-1 drugs or combined ICI.[9] The estimated prevalence of arthralgia with pembrolizumab is estimated at 9–12% but may run unnoticed. Arthralgia typically affects large joints symmetrically[9] and tends to occur around the third or sixth month after the beginning of immunotherapy. Serological markers such as rheumatoid factor, citrullinated peptide antibody or CK levels are generally not elevated.[9]

Managing irAEs can often be achieved without discontinuing immunotherapy, but it requires maintaining the prednisone dosage <10 mg/day (or equivalent) to avoid compromising its efficacy.[4] Some irAEs can persist despite treatment discontinuation. While the Cancer Immunotherapy Society recommends the use of disease-modifying antirheumatic drugs, hydroxychloroquine is not currently mentioned as a potential corticosteroid-sparing agent.[6]

In conclusion, whether used as monotherapy or as an adjuvant therapy hydroxychloroquine appears to be a safe and effective option to address musculoskeletal symptoms without compromising the efficacy of immunotherapy. Further studies are needed to validate its role in managing these patients.

Conflict of interests

The authors state that they have no conflict of interests.

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