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Clinical Course of Hypertrophic Pulmonary Osteoarthropathy in a Patient Receiving Immune Checkpoint Inhibitor Therapy

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Introduction

Several paraneoplastic syndromes are associated with lung cancer; often, these manifest well after the diagnosis is established. Here, we describe a case of lung adenocarcinoma heralded by knee pain that was eventually diagnosed as hypertrophic pulmonary osteoarthropathy (HPOA) and treated with combined modality therapy including immune checkpoint inhibitors (ICIs). HPOA is a rare condition that can affect patients with non–small-cell lung cancer (NSCLC).¹ It is characterized by increased angiogenesis, edema, and excessive connective tissue deposition in the periosteum of tubular bones.² Very little data exist to guide its management, and to our knowledge, neither the use of hydroxychloroquine to treat pain secondary to HPOA nor outcomes of HPOA during ICI treatment have previously been reported.

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Disclosure

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

Case Report

A 57-year-old woman with a remote history of stage II breast cancer treated with surgery, chemotherapy, and chest wall radiation 7 years previously, and active long-term tobacco use, presented to her primary care doctor with 4 months of severe, progressive bilateral knee pain. Physical exam showed mild bilateral medial joint line tenderness and slight right patellar apprehension. Serologic testing demonstrated elevated C-reactive protein (30 mg/L) and erythrocyte sedimentation rate (53 mm/hr), negative rheumatoid factor and anti-cyclic citrullinated peptide antibody, and slightly positive anti-nuclear antibody (1:160). X-rays were normal. The pain continued to worsen despite physical therapy, nonsteroidal anti-inflammatory drugs, and intra-articular corticosteroid injections.

She underwent bilateral knee magnetic resonance imaging, which showed periosteal reactivity involving the distal femurs consistent with HPOA^{3,4} (Figure 1). She also reported a new cough and 25-pound weight loss, and physical exam revealed clubbing of the fingers. Computed tomography (CT) of the chest revealed a 5 × 7 cm left upper lobe lung mass. Biopsy revealed adenocarcinoma of lung origin. Bronchoscopy and endobronchial biopsy with ultrasound revealed a single positive N2 node (4L). Epidermal growth factor receptor mutation and anaplastic lymphoma kinase rearrangement testing were negative, and programmed death-ligand 1 expression was < 1%. Magnetic resonance imaging of the brain and CT of the abdomen and pelvis showed no metastases.

She underwent 4 cycles of neoadjuvant chemotherapy with carboplatin and pemetrexed for stage IIIB disease, and her knee pain improved markedly. Cisplatin was not given owing to baseline hearing loss requiring hearing aids. She was taken to the operating room for left upper lobectomy, but this was aborted as the tumor was grossly unresectable owing to chest wall invasion not visible on CT imaging. During this time, her knee pain worsened. Repeat C-reactive protein (139.6 mg/L) and erythrocyte sedimentation rate (56 mm/hr) were elevated at levels higher than her initial presentation. Methadone, dexamethasone 2 mg daily, and oxycodone for breakthrough pain were initiated, but despite escalating doses of oxycodone, severe pain persisted. Dexamethasone was uptitrated to 3 mg daily, and hydroxychloroquine 200 mg daily was added. With these medication changes, pain control slowly improved. We also considered bisphosphonates, which have shown efficacy for treatment of pain secondary to HPOA.^{1,5}

The patient was initially considered not to be a candidate for definitive chemo-radiation treatment for T3N2, stage IIIB disease owing to prior chest wall radiation therapy administered for breast cancer. She received 1 cycle of chemo-immunotherapy with carboplatin, pemetrexed, and pembrolizumab. After close review of her case, chemo-radiation with hyperfractionated radiation (60 Gy in 50 twice-daily fractions, to minimize toxicity) was felt to be a safe treatment option. She started definitive chemo-radiation with concurrent carboplatin and paclitaxel. She experienced a partial response (39% decrease in disease burden) (Figure 2), and her pain improved significantly. She was weaned off opioids; dexamethasone and hydroxychloroquine were stopped. She is presently receiving consolidation therapy with durvalumab. She has not experienced even temporary worsening

of her musculoskeletal symptoms with administration of 2 different ICI drugs, suggesting that her HPOA has not flared with the anti-tumor T-cell response that ICIs may induce.

Discussion

The pathophysiology of HPOA in lung cancer is likely multi-factorial and remains poorly understood. Right-to-left shunting permits megakaryocytes and platelet clumps to avoid trapping in the pulmonary vasculature, allowing them to travel to small, distal vessels and release growth factors that promote fibroblast proliferation and angiogenesis, including vascular endothelial growth factor.⁵ Elevated circulating levels of this protein, a treatment target in NSCLC, have been associated with HPOA.² There is also evidence that the process of platelet maturation and release of platelet-derived growth factor in the setting of platelet aggregation contributes to the pathophysiology of HPOA.⁵ Programmed death-ligand 1 has also been found to be expressed by platelets, and treatment with ICIs may impact platelet count and function.⁶

HPOA has been associated with chronic infections, immunodeficiency, and inflammatory bowel disease,^{4,5} suggesting a possible immune-based etiology that could be affected by immunomodulating agents such as ICIs. If HPOA is triggered by immune suppression, it could be postulated that direct stimulation of the immune system with ICIs would improve symptoms. Conversely, if HPOA itself is an inflammatory process, although the optimal treatment for HPOA is to address the primary tumor, the potential for causing flare of HPOA symptoms owing to ICI therapy may affect clinical decision-making in the absence of documented safety in the literature. In this case, the patient was able to tolerate ICI therapy in 2 different settings (in combination with chemotherapy and as consolidation treatment after chemoradiation) without affecting her HPOA symptoms. This case offers some reassurance that ICI therapy is safe in patients with NSCLC and HPOA and should be utilized if warranted.

Another aspect of this case to highlight is the novel use of hydroxychloroquine. This antimalarial drug, typically used in the treatment of autoimmune diseases, interferes with antigen presentation by macrophages and dendritic cells through alteration of the pH of lysosomes in these cells, which prevents processing of antigens and linkage to major histocompatibility proteins.⁷ The use of hydroxychloroquine to treat pain secondary to HPOA has not previously been reported. Its apparent efficacy as an adjunct in controlling pain that was refractory to dexamethasone and escalating doses of opioids further supports a role of the immune system in the pathophysiology of HPOA that remains to be understood. However, the complex clinical scenario – including use of multiple medications at increasing doses – makes definitive conclusions regarding efficacy challenging.

Conclusion

This case illustrates how an uncommon paraneoplastic syndrome might present in the form of a common musculoskeletal complaint, even before malignancy is diagnosed. To our knowledge, the clinical outcomes of patients with HPOA treated with ICIs have not been previously reported. At least in this case, the lack of any flare of symptoms during ICI

treatment is reassuring and should not preclude the use of these agents in patients with HPOA.

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Clinical Practice Points

- Hypertrophic pulmonary osteoarthropathy (HPOA) is a well-known paraneoplastic syndrome associated with lung cancer, and some have hypothesized that its pathophysiology is immune-mediated. However, the clinical course of symptoms from this syndrome during treatment with immune checkpoint inhibitors (ICIs) has not previously been described, and effective treatments for pain secondary to HPOA have not been fully elucidated.
- We present the case of a patient who was diagnosed with HPOA involving the bilateral distal femurs causing severe pain and subsequently found to have adenocarcinoma of the lung. We describe changes in her symptoms during multiple lines of treatment, including ICIs, and we discuss effective strategies for pain management for this condition. The patient's pain improved with regression of her tumor burden after treatment with chemotherapy, combined modality chemotherapy-radiation, and immune checkpoint inhibition. Importantly, her pain did not flare even temporarily with administration of ICIs. Severe episodes of pain prior to initiating treatment and during periods of cancer progression were managed effectively with opioids, dexamethasone, and hydroxychloroquine, the use of which has not been previously described for this condition.
- This case provides evidence that ICIs do not worsen symptoms of HPOA, despite their stimulation of an anti-tumor immune response, supporting their use in patients with this condition. It also provides support for the possible efficacy of hydroxychloroquine for treatment of pain secondary to HPOA in conjunction with other therapies.

Figure 1.

Coronal T1 (A) and Intermediate-weighted, Fat-Saturated (B) Images of the Left Knee. The Orange Arrows Depict Linear, Low to Intermediate T1 Signal, Corresponding to High Signal Changes on the Water-Sensitive, Intermediate-weighted Image Along the Surface of the Distal Femoral Metaphysis, Representing Smooth Circumferential Periosteal Reaction of the Distal Femur. The Bone Marrow Signal is Normal. There is No Periosteal Reaction of the Visualized Tibia. Symmetric Findings on Magnetic Resonance Imaging of the Right Knee (Not Shown) Support the Diagnosis of Hypertrophic Pulmonary Osteoarthropathy

Figure 2.

A, Axial Image From Initial Staging Chest Computed Tomography (CT) Depicts a Large Mass in the Centered in the Left Upper lobe. The Mass Extends From the Hilum to the Anterolateral Pleural Surface. This Mass was Biopsied Under CT Guidance and Shown to be Pulmonary Adenocarcinoma. B, Axial Image From Restaging Chest CT 1 Year Later Shows a Partial Response to Therapy With a Decrease in Size of the Mass Lesion