CLINICAL VIGNETTE

Pembrolizumab Associated Concurrent Pneumonitis and Vasculitis

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Case Report

A 40-year-old female presented with clinical stage IIIC1 squamous cell carcinoma (SSC) of cervix after one year of irregular vaginal bleeding and pelvic pain. She had a large cervical mass on exam and biopsy confirmed poorly differentiated SCC. Staging positron emission tomogram (PET) scan showed diffusely fluorodeoxyglucose (FDG) avid uterus with 6.8 cm cervical mass with high FDG avidity, and evidence of extension into the vagina. There were also 2.5cm right pelvic lymph nodes (LN) and 2 small hypermetabolic LNs anterior to the right psoas. She was treated with concurrent chemoradiation with weekly cisplatin as radiation sensitizer, followed by brachytherapy. Restaging PET two months after treatment showed interval development of enlarged para-aortic lymph-adenopathy. She received 3 cycles of carboplatin/paclitaxel with significant decrease in size of the retroperitoneal lymph node conglomerate. Her case was presented at our tumor board which recommended radiation for her oligometastatic disease site at the nodal conglomerate. Weekly carboplatin/paclitaxel was given as radiation sensitizer and she completed treatment nine months later. One year after treatment, restaging PET showed new oligo-progression in her left supraclavicular node with FDG uptake. Her prior treated area in the abdomen showed interval decrease of the small para-aortic lymph node conglomerate without FDG uptake. Her PDL1 combined positive score (CPS) was 10%. She proceeded with stereotactic body radiative therapy (SBRT) to the left supraclavicular site followed by one year of "adjuvant" pembrolizumab. She received 8 cycles of pembrolizumab over six months and developed pembrolizumab associated thyroiditis mid cycle, found on screening TSH and T4. Her thyroid function corrected with replacement and interval PET showed no disease progression. She developed acute shortness of breath with oxygenation of 65% on room air after cycle 9. Emergent computed tomography pulmonary angiography (CTPA) at the local hospital showed no pulmonary embolus (PE) but bilateral infiltrates concerning for pembrolizumab induced pneumonitis. She responded to high dose intravenous (IV) methylprednisolone with improved breathing. Exam revealed bilateral dusky colored fingers and Rheumatological evaluation was initiated. Findings included mild elevation of antinuclear antibody (ANA) with negative Lupus panel and cryoglobulin levels. She did not require oxygen and was discharged home on prednisone. She then developed worsening pain and dusky color changes in her fingers over two weeks despite high dose steroids. She started a slower steroid taper in addition to sildenafil and mycophenolate mofetil and symptoms eventually resolved over 6 months. She has not been rechallenged with pembrolizumab and her restaging scans continued to show no evidence of disease for over 2 years.

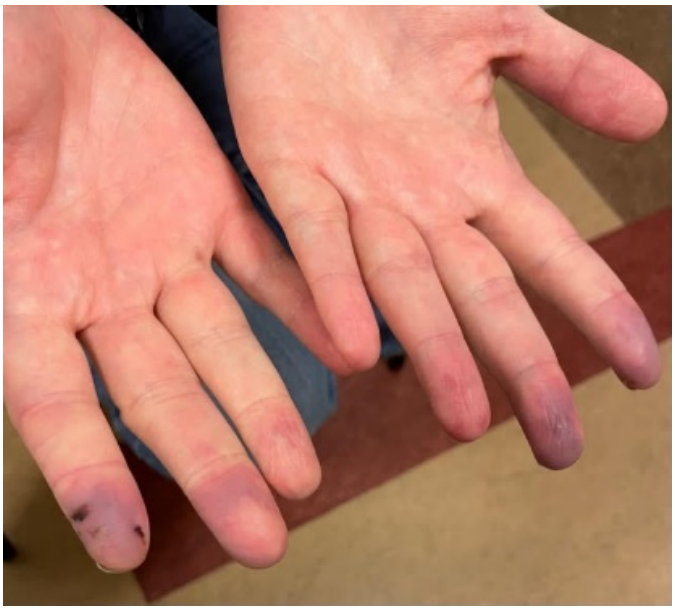

Figure 1. Bilateral fingers are painful with dusky color at time of presentation.

Discussion

Pembrolizumab is an immune checkpoint inhibitor shown to improve survival in melanoma, lung, bladder and many other solid tumors.[1] It can trigger immune related adverse reactions by impacting patient's immune system. Immune related adverse reactions of pembrolizumab include pneumonitis, colitis, hepatitis, endocrinopathies and nephritis.[2] Vasculitis is a rarely-reported immune-related adverse event associated with immune checkpoint inhibitors involving blood vessels.[3] A recent review by Daxini et al reported 20 out of 53 confirmed cases of immunotherapy induced vasculitis were large vessel vasculitis.[4] All resolved after either holding immune checkpointing inhibitors or starting steroids.

Our patient most likely had small vessel vasculitis induced by pembrolizumab. She did not have any well-defined connective tissue disorder in association with her Raynaud's. Her symptom may reflect generalized autoimmunity induced by pembrolizumab. She had mild elevation of her ANA. Interestingly, onset

of her symptoms started after over six months of pembrolizumab. Onset of rheumatic immune related adverse effects have been reported from 2 to 13 months after initiation of check point inhibitor therapy.[5] She remained refractory despite discontinuation of pembrolizumab and high dose of IV/oral steroids.

Increasing numbers of cancers are being treated with immune checkpoint inhibitors and the incidence of treatment induced vasculitis will likely increase. Recognizing the risk and management of immune checkpoint inhibitor induced vasculitis is crucial. One reported case of ipilimumab induced digital ischemia required amputations, further illustrating the importance of prompt recognition of this adverse effect.[6] It requires close collaboration between treating oncologists and rheumatologists.[7]

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