CLINICAL VIGNETTE

Radiation Recall with Nivolumab

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A 53-year-old male initially presented with increasing left neck mass 15 years ago. PET scan showed increased activity in left tonsillar area as well as, the left neck mass and biopsy of both yielded squamous cell carcinoma. He had prior tonsillectomy as a child. He underwent definitive radiation and received 7740 centi gray to oropharynx and bilateral neck along with unspecified chemotherapy. Subsequent left neck lymph node dissection and left tonsillar area biopsy showed no residual carcinoma.

Ten years later he developed persistent sore throat, followed by progressive dysphagia, weight loss and dysphonia. He was eventually diagnosed with squamous cell carcinoma of the cervical esophagus, extending over 5 centimeters from the cricoid causing severe stenosis. PET scan showed a hyperactive metabolic circumferential mass around the cervical esophagus as well as para-esophageal and superior mediastinal adenopathy. He received 7440 centi gray to the cervical esophagus and mediastinum along with 2 cycles of cisplatin and 5FU, concurrent with radiation 4 weeks apart. Gastric tube (G-tube) was placed prior to treatment. Subsequent evaluation showed no residual cancer but persistent severe stenosis of cervical esophagus despite multiple dilatation attempts. He remains dependent on G-tube for nutrition, hydration, and medications. He was followed with regular exams and periodic scans.

Three years later PET scan showed a new hyper metabolic mass in the superior mid pole of the right kidney measuring 5.9 x 5.2 cm, and 11x16 mm hypermetabolic right hilar lymph node as well as asymmetric uptake in left posterior mandibular area corresponding to molar tooth #16. EGD and pan endoscopy did not show any malignancy. Right nephrectomy revealed a 5.9 cm metastatic squamous cell carcinoma to the right kidney. He was started on immunotherapy with Nivolumab 240 mg every two weeks for metastatic squamous cell carcinoma of head and neck origin. He also noted increasing pain at the base of tongue and molar area. PET scan showed further increase in activity at the left posterior mandible extending to the left retromolar trigone, palatine tonsillar area and glossopharyngeal sulcus measuring 14x16 mm. In addition there was increase size of the left hilar lymph node. Biopsy of the area of concern in mouth confirmed squamous cell carcinoma. He continued on Nivolumab 240 mg every 2 weeks during this time, receiving lower doses. Because of the concern for progression in left molar area, Nivolumab was stopped and he underwent radiation 6480 centigray to gross tumor area at base of tongue and molar areas along with 5 weekly doses of cisplatin. He had mild mucositis during treatment managed with magic mouthwash. He continued to use his G-tube for most nutrition and medications. He also received nystatin mouth rinse with resolution of mucositis and good local response after completing radiation.

One month after completing radiation, Nivolumab was restarted at same dose and schedule. Two weeks later, he reported sores in his mouth with a viral appearance, treated with Vancyclovir. Despite antiviral therapy he developed worsening mucositis with painful mouth and throat sores and painful cracked bleeding lips. His symptoms did not respond to increased frequency of magic mouth wash. Immunotherapy was stopped and he was aggressively supported with dexamethasone mouth rinses, scheduled magic mouthwash and systemic antiviral and antifungal medications through G tube. Despite aggressive management he had worsening symptoms of mouth and throat inflammation and increased pain at the mouth tumor site. PET scan again showed increased activity at tumor site in left tonsillar area. As symptoms of severe mucositis persisted 8 weeks after stopping Nivolumab with maximum supportive care, the clinical diagnosis of radiation recall by immunotherapy was made. He was started on prednisone at 1 mg / Kg through G-tube. After starting prednisone his mucositis symptoms and pain at tumor site completely resolved in 2 weeks. At that time, he was slowly tapered to lower dose prednisone. When dose of prednisone was lowered to 5 mg every other day his symptoms of early mucositis returned in mouth which again responded to increasing dose of prednisone. Repeat PET scan showed significant improvement of tumor site at left tonsillar area (which is being confirmed by endoscopy) and stable activity and size of left hilar lymph node and no new disease.

Mucositis is breakdown of rapidly dividing epithelial cells leaving the mucosal lining open to ulceration and infection. Mucosal tissues including associated mucus secreting glands are affected. Mucous membranes become red, swollen with painful sores, white patches, bleeding areas and thickened saliva which affects nutrition and dental health. Radiation mucositis is caused by free radical generation and DNA damage starting within one week of start of radiation and usually resolving in 1-6 weeks after stopping. Beside total cumulative dose and fractionation, size and location of field of radiation and concurrent chemotherapy affect risk. Floor of mouth, palate and tongue are especially sensitive. Dental health, hypo salivation and previous treatments also increase risk. The damaged area has decreased antimicrobial defense and infection can also delay healing.[1,2]

Radiation recall is an acute inflammatory reaction confined to previously irradiated areas usually triggered by chemotherapy. This is unpredictable and occurs in less than 10% of patients. Although skin is most often affected, multiple other irradiated areas can be affected and it can happen weeks to years after radiation is completed. Beside chemotherapy, multiple agents directed against MTOR, EGFR, HDAC, BRAF, CDK, VEGF and Her2 targets have been reported. Rarely antiestrogen and even non-cancer drugs such as antibiotics have also been reported to cause radiation recall. Case reports of Nivolumab causing radiation recall dermatitis and pneumonitis have been recently described.[3,4]

Nivolumab is an anti–PD1 monoclonal antibody approved for treatment of head and neck squamous cell recurrent or metastatic carcinoma in addition to multiple other cancers. Majority of the described toxicities are mediated through immune directed injury to non-cancer cells elsewhere. Although skin and thyroid are most commonly affected, potentially any tissue/or organ can be affected. Toxicity is usually managed by interruption of treatment, supportive care and systemic steroids.[5,6]

Recent data shows synergy between immunotherapy and radiation therapy. This is thought to occur because radiation increases the expression of target antigens by the tumor cells and making them more available for immunotherapy. The enhanced effect and specificity of immunotherapy to targeted tumor antigens has been demonstrated in areas of radiated tumor and also tumors outside of radiation field which have been reported to regress. This synergy may also increase the toxicity of radiation and combining these two modalities may require alteration of dose and field of radiation. Conformational fields limited to gross tumor, lower total dose and fewer fractions at higher dose per fraction are suggested.[7-10]

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Submitted August 21, 2018