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Teaching Case

Integrating radiation therapy with emerging systemic therapies: Lessons from a patient with cerebral radionecrosis, spinal cord myelopathy, and radiation pneumonitis

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Case Report

A 14-year-old male received four cycles of ipilimumab (3 mg/kg every 3 weeks) for stage IV BRAF V600E mutation-positive melanoma having progressed on dacarbazine chemotherapy and predating first-line use of BRAF inhibitors in the United Kingdom. He developed bulky symptomatic mediastinal nodal disease and switched to the BRAF-inhibitor dabrafenib 150 mg twice daily 6 months after completing ipilimumab. Despite initial response, he represented with critical airway stenosis 15 months later, warranting urgent palliative radiation therapy. This was delivered using 11 × 11 cm parallel opposed and equally weighted anterior and posterior 10-MV fields at the level of the T4-T7 vertebrae (Fig 1). The prescribed dose was 17 Gy at midplane in 2 fractions 7 days apart. The spinal cord dose ranged between 102% (17.3 Gy) inferiorly and 105% (17.9 Gy) superiorly. The interval between ipilimumab and radiation therapy was 20 months. He received dabrafenib up to and including the first day of radiation therapy. He received 5 further days of dabrafenib commencing 4 days after radiation therapy was completed.

One month later, he received stereotactic radiosurgery (SRS) to 4 asymptomatic brain metastases 5.80, 0.82, 0.07, and 0.03 cm^3 in size. Isotropic expansions of 1-2 mm were performed to create planning target volumes (PTVs) 8.58, 2.88, 0.50, and 0.35 cm^3, respectively. The prescribed dose to the 80% isodose encompassing each PTV was 18 Gy for the largest PTV and 21 Gy for the others. The associated 12-Gy volume (including PTV) for each lesion was 21.6, 9.73, 2.49, and 1.60 cm^3, respectively.

Four weeks later he commenced adoptive cell therapy for progressing thoracic disease using tumor-infiltrating

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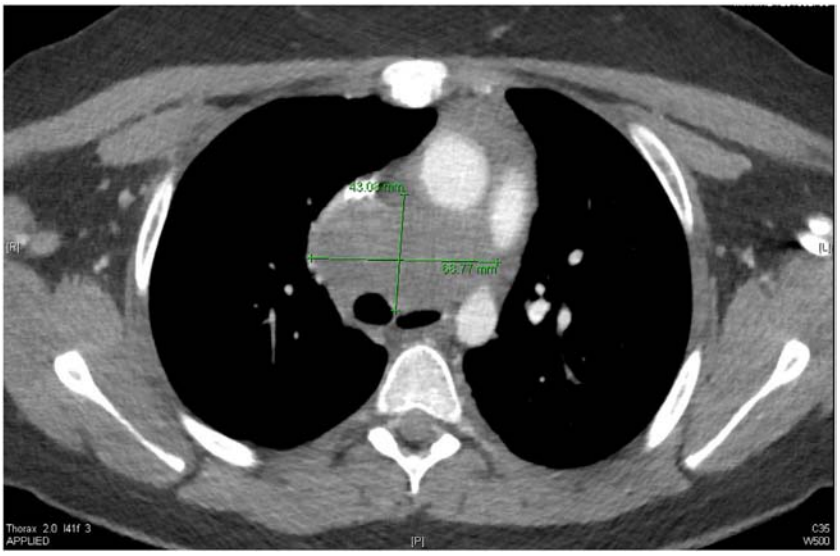

Figure 1 Contrast-enhanced computed tomography axial view at T4 level demonstrating large mediastinal nodal mass necessitating urgent radiation therapy.

lymphocytes (TIL). He received standard preconditioning with 4000 mg cyclophosphamide (60 mg/kg) for 2 doses and 44 mg fludarabine (25 mg/m^2) for 3 doses. Chemotherapy was reduced because of his generally weak condition. He then received high-dose interleukin-2 at 45 million IU for 6 doses and 18 million IU for the final 2 doses. He received 2.2×10^{10} TIL cells, with rapid lymphocyte engraftment. Following TIL therapy, an untreated cerebellar metastasis radiologically progressed before responding. The thoracic disease regressed slowly to complete remission after 18 months without further therapy.

Six weeks after thoracic radiation therapy, he developed mild dyspnea and paramediastinal ground-glass opacification at the level T4-T7 consistent with localized radiation pneumonitis (Fig 2) that resolved without treatment. Three months after thoracic radiation therapy, he began experiencing difficulty in walking, which progressed to complete paraplegia with sensory loss below the T7 dermatome over 4 weeks despite bevacizumab (5 mg/kg). Magnetic resonance imaging demonstrated heterogeneous enhancement within the spinal cord at T4-T7 consistent with radiation myelitis (Fig 3). On serial magnetic resonance brain imaging increased contrast enhancement slowly developed within each of the areas treated with SRS. Following a partial seizure, tumor progression was suspected, and he underwent surgery to the lesion that was the second largest at the time of SRS. Histopathology confirmed radionecrosis and no malignancy. Three years after SRS, he remains paraplegic but otherwise well with no active disease.

Discussion

Targeted and immunological systemic agents have emerged as first-line treatments for most patients with

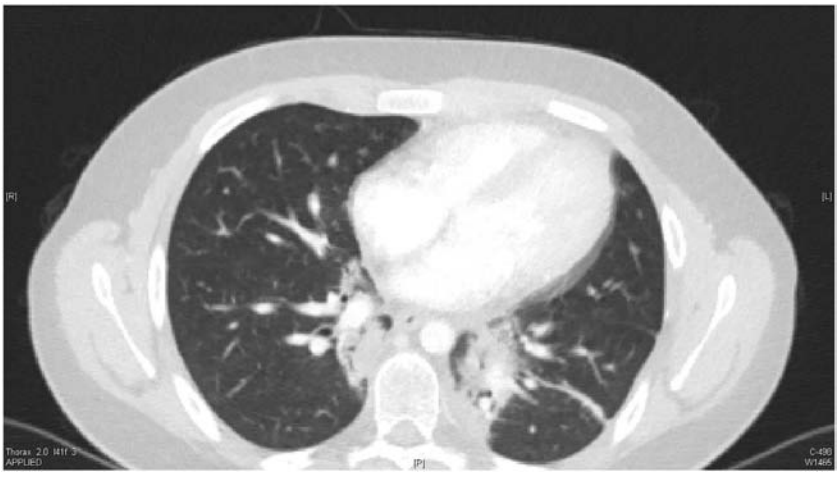

Figure 2 Contrast-enhanced computed tomography axial view at T6 level demonstrating radiation pneumonitis.