Teaching Case

Osteoradionecrosis of the jaw in a patient with lymphoma treated with rituximab and concomitant involved field radiation therapy

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Introduction

Most guidelines recommend radiation therapy for the treatment of early stage (I/II), grade 1-3A follicular lymphoma (FL).[1,2] This recommendation is mostly based on retrospective studies in the pre-rituximab era, showing long-term disease-free survival with extended field radiation therapy and subsequently involved field radiation therapy (IFRT).[3-8]

Ongoing studies are currently exploring the potential benefit of combining systemic with localized treatment. The MIR trial was a prospective study conducted by the German Low-Grade Lymphoma Study Group and the German Radiation Oncology Group, in which patients with early stage CD20 positive grade 1 or 2 FL were treated with IFRT (either 30 or 40 Gy) and concomitant rituximab. Preliminary data reported at the 2012 Annual Meeting and Exposition of the American Society of Hematology and the 2014 European Society for Radiotherapy and Oncology Congress showed a 2-year progression-free survival (PFS) rate of 89%, which approximated outcomes that have been seen historically with extended field radiation therapy and surpassing outcomes of IFRT.[9,10] Additionally, retrospective

studies with rituximab before or after IFRT have shown improvements in PFS compared with IFRT alone.[11,12]

Osteoradionecrosis (ORN) of the jaw is one of the most severe chronic side effects of radiation therapy to the head and neck region. Risk of ORN is believed to be directly related to radiation dose and strongly associated with doses >60 Gy.[13] Concomitant radiosensitizing chemotherapy, such as with platinum analogues, may be an additional risk factor.[14] To our knowledge, there have been no reports of ORN at radiation doses <45 Gy with IFRT.

Here, we present the case of a patient treated according to the MIR trial protocol, who received concomitant rituximab and IFRT at a dose of 30.6 Gy and subsequently developed ORN of the jaw.

Case

A 70-year-old woman with a history of diabetes, hypertension, atrial fibrillation, chronic kidney disease stage 3, 14-pack-years of active smoking, and chronic obstructive pulmonary disease was referred to the oncology service for a mass on the right parotid gland that had been present for several months, along with 20 lb weight loss and night sweats.

The patient underwent a fine needle aspiration of the mass that showed cells with aberrant mature B-cell immunophenotype suspicious for CD10 + lymphoma
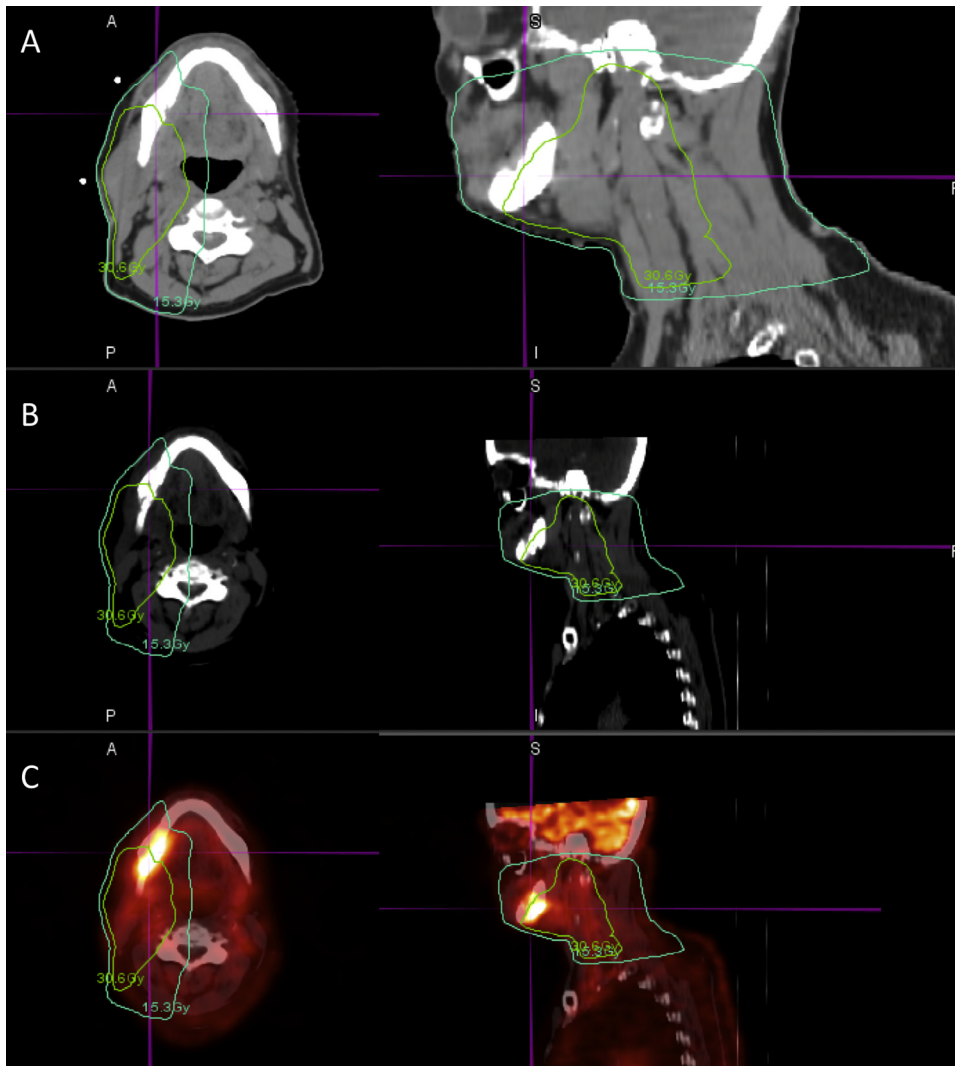

Figure 1 Baseline computed tomography (CT) prior to involved field radiation therapy with 30.6 Gy (light green) and 15.3 Gy (blue) isodose lines (A), posttreatment CT imaging 11 weeks after completion of involved field radiation therapy showing evidence of radiation necrosis on CT (B), and positron emission tomography/CT (C) with a standardized uptake value of 6.5.

and subsequently a parotid mass excisional biopsy that showed a CD5-/CD10 + low grade B-cell lymphoma (Ki67 5-10%) that was positive for CD20, consistent with grade 1-2/3 FL.

Bone marrow biopsy showed no morphologic or immunophenotypic evidence of involvement by B-cell lymphoproliferative disorder. Positron emission tomography/computed tomography (PET/CT) imaging showed a fluorodeoxyglucose (FDG)-avid mass in the right parotid gland/right level II cervical region but no evidence of FDG-avid malignancy elsewhere in the field of view (Fig 1a). There was enlargement of the left adrenal gland and nodular thickening of the right adrenal gland consistent with adenomatous hyperplasia. The patient was diagnosed with stage IB$_E$ disease.

On the basis of the reported encouraging preliminary results, the patient was treated per the MIR protocol with a combination of rituximab and radiation therapy.[10] The MIR protocol involves an initial block of 4 weekly rituximab treatments (375 mg/m^2) followed by a 4-week treatment gap and restaging PET/CT on week 7. Subsequently, a series of 4 weekly rituximab infusions is given concurrently with IFRT at a dose of 40 Gy for residual disease or 30 Gy if in complete remission.

The patient completed the first block of rituximab treatment and had a partial response with a palpable residual mass in the right parotid gland/right level II cervical region, consistent with the known primary malignant mass. Subsequently, she completed the second block of rituximab and IFRT. Despite a partial response, 30.6 Gy in 17 fractions was administered due to the patient's comorbidities and on the basis of data from the British National Lymphoma Investigation study, which showed that 24 Gy in 12 fractions was as effective for local control as 40 Gy in 20 fractions.[15] The radiation therapy course was complicated by severe mucositis 1 week after treatment.

Two months after finishing the second block of treatment, the patient reported mild bleeding and pain in the right jaw that was worse with eating and had been present for 1 month. Physical examination was remarkable for a receding gum to the right lower jaw; gum ulceration with exposed bone and tenderness to palpation were noted. A follow-up PET/CT scan showed marked improvement in the previously described hypermetabolic right parotid gland mass consistent with complete metabolic response; however, new fragmentation and cortical irregularity of the body of the right mandible was noted with associated adjacent soft tissue swelling and FDG uptake (Fig 1b and c).

The patient was evaluated by dental, medical, and radiation oncology and, although no biopsy was performed, she was diagnosed with ORN of the right jaw. She was treated with a course of antibiotics and nonsteroidal anti-inflammatory drugs with complete resolution of her symptomatology, without requiring debridement. A magnetic resonance imaging scan of the neck for an unrelated indication 4 months later showed loss of normal marrow signal along the course of the right mandible corresponding to the prior PET/CT findings.

Discussion

ORN of the jaw is more commonly seen in patients receiving radiation at doses >60 Gy.[13,14] It has not to date been described as a side effect of IFRT monotherapy at doses <45 Gy.[15,16] In addition to the radiation dose, there are additional reported risk factors for ORN in patients with head and neck cancers, such as smoking, concomitant radiosensitizing chemotherapy (e.g., platinum analogues), male sex, bone surgery immediately preceding radiation therapy, use of bisphosphonates, and poor dental hygiene.[14,17]

ORN can develop anytime between 2 to 98 months, although it is usually seen 3 to 5 years after the end of radiation therapy.[17,18] In a recent report by The Memorial Sloan Kettering Cancer Center group on patients with head and neck cancer, the median time from radiation to ORN development was 19.1 months, with a range of 0 to 220.2 months. Our patient developed ORN of the jaw within 2 months from the end of radiation therapy. Although earlier than average, the timing of ORN manifestation in our patient was still within the range previously reported.[19]

The patient in this report received low-dose radiation (30.6 Gy) and although she had been an active smoker, she did not have any of the other aforementioned risk factors for ORN. She was edentulous and required no dental intervention. Our patient received rituximab in conjunction with radiation to the parotid gland. There have been limited case reports of osteonecrosis with rituximab treatment alone; however, in none was rituximab identified as a clear culprit, and the postulated mechanism of an antiangiogenetic, apoptotic effect remains hypothetical.[20,21] More interestingly, the simultaneous exposure of lymphoma cells to rituximab and ionizing radiation have been shown to markedly enhance apoptosis and cell growth delay, suggesting a rituximab radiosensitizing effect in vitro.[22,23]

Rituximab has a prolonged half-life and has been extensively used in conjunction with radiation in the treatment of lymphoma as part of the rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone (R-CHOP) regimen.[24] In contrast to what one would expect in the context of a rituximab radiosensitizing effect, there are no prior reports of ORN after R-CHOP followed by consolidative or adjunctive radiation therapy. The blood supply of the mandible could make it particularly susceptible to avascular necrosis, and cases of R-CHOP chemotherapy followed by radiation in the proximity of the jaw may be overall infrequent. There could also be a dose-dependent radiosensitizing effect, which could explain the additional risk when rituximab is given concurrently with radiation.

Conclusions

Our patient was treated with concurrent IFRT and rituximab and developed jaw ORN despite the low dose of radiation used. No additional ORN risk factors were identified except for smoking. It is possible that the toxicity experienced by our patient at a radiation dose not previously associated with ORN was due to a rituximab radiosensitizing effect.

In the interim analysis of the MIR trial, of the 85 patients who were included in the study, 19 experienced adverse events, including 4 labeled as bone injuries, albeit not specified.[9] From personal communication with the leading author, no ORN was seen and all bone events were unrelated to treatment.

Although the mature results of the now completed MIR trial are awaited, further information regarding the safety of concurrent rituximab and radiation needs to be cautiously collected. Ongoing prospective trials in early stage FL (one at MD Anderson Cancer Center [NCT01473628] where IFRT with concomitant rituximab is being compared with IFRT alone, and another by the Trans-Tasman Radiation Oncology Group comparing IFRT with IFRT combined with rituximab and chemotherapy [NCT00115700]) will help shed light on the potential of rare toxicities with this combination. Until then, the association of ORN with this otherwise promising therapeutic strategy remains to be determined and quantified.

Finally, a possible rituximab radiosensitizing effect and its mechanism need to be further elucidated because such an effect can have significant clinical implications in terms of both treatment efficacy and toxicity.

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