Esophageal Stricture Following Radiation, Concurrent Immunochemotherapy, Treated With Hyperbaric Oxygen and Dilation

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Abstract

Low-dose palliative radiation may offer symptomatic relief in patients with spinal metastases from primary renal cell cancer and is unlikely to result in radiation injury. Patients with advanced malignancy requiring palliative radiation are often also receiving chemotherapy. Synergistic adverse effects resulting from combined palliative radiation and novel antiprogrammed cell death-1 (anti-PD 1) and/or multityrosine kinase inhibitors are rare.

We report about a 60-year-old woman with metastatic clear-cell renal cancer, status post-left nephrectomy, with debilitating mid-back pain from metastatic tumor burden and foraminal nerve compression. Her chemotherapeutic regimen was repeatedly altered because of progression of disease until she was maintained on the anti-PD 1 checkpoint inhibitor, nivolumab. She received palliative radiation to her thoracic spine over a 2-week period, and nivolumab was then switched to cabozantinib midway through a course of palliative radiation. The patient rapidly developed severe esophagitis, progressing to esophageal stricture, and required placement of a percutaneous endoscopic gastrostomy tube. She was successfully treated with serial esophageal dilation and hyperbaric oxygen treatments to diminish inflammation and improve tissue vascularity. Concurrent use of anti-PD 1 and/or multityrosine kinase drugs may accelerate development of radiation injury regardless of radiation dosage. Radiation-induced esophageal stricture was managed successfully in this patient with serial esophageal dilation and adjuvant hyperbaric oxygen.

We present the case of a patient with esophageal stricture caused by palliative radiation for metastatic renal cell cancer and worsened by concurrent antiprogrammed cell death (PD) receptor and tyrosine kinase inhibitor medications, that was successfully treated with serial dilation and adjuvant hyperbaric oxygen (HBO) therapy. Palliative radiation and concurrent immune checkpoint inhibitors with or without chemotherapy have led to improved survival rates among patients with metastatic renal cell cancer.[1−3] Clinical studies suggest concurrent radiation and chemotherapy regimens portends increased acute and chronic adverse radiation events.[4,5] Esophageal stricture is a well-recognized late adverse event of head, neck, or thoracic radiation, but it is uncommon to have a stricture develop following palliation-level doses of radiation (≤30 Gy).[6,7] Serial esophageal dilation has proved to be relatively successful in treating radiation-induced esophageal strictures, but recurrence remains problematic.[8,9] Gradually, over time, irradiated tissue becomes hypoxic, hypovascular, and hypocellular.[10] HBO improves tissue oxygenation, stimulates vasculogenesis, and angiogenesis, thereby creating a tissue bed ready for healing.[11,12] Hyperbaric oxygen has thus been shown to

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facilitate healing resulting from radiation-induced injury in non-neural tissue.[13]

CASE

A 60-year-old woman with clear-cell renal cancer status post-left nephrectomy presented with metastatic disease to the thoracic spine and lungs 10 years following her initial diagnosis. She did not respond favorably to a chemotherapy regimen consisting of HD-interleukin-2, sorafenib, and pazopanib and had evidence of disease progression to the thoracic spine. The patient was subsequently treated with nivolumab as second-line therapy and underwent OsteoCool ablation (Medtronic, Minneapolis, MN) and kyphoplasty. The patient presented 6 months later with recurrent severe back pain. Restaging cross-sectional imaging studies showed metastatic tumor burden with nerve compression and invasion of spine, paraspinal metastasis with extension into the right neural foramina of the T10-T11 and T11-T12, causing significant stenosis. She was maintained on nivolumab and offered palliative thoracic radiation. The patient also received a total of 30 Gy to her thoracic spine via external-beam radiation over a 2-week period. On day 6 of radiation therapy, nivolumab was discontinued, and she was switched to cabozantinib.

During the second week of radiation therapy, she experienced severe dysphagia and odynophagia, requiring inpatient care for an inability to tolerate oral intake. An esophagogastroduodenoscopy (EGD) showed evidence of diffuse desquamation and ulceration of the mucosa in the mid- and distal esophagus consistent with severe radiation esophagitis. She was treated with high-dose acid-suppression therapy, with a combination of proton-pump inhibitors and histamine-2 receptor blockers. She required placement of a percutaneous endoscopic gastrostomy (PEG) tube for nutritional support. Repeat upper endoscopies performed at 3 and 5 months after receiving radiation therapy showed ongoing evidence of refractory radiation esophagitis with ulceration. Other etiologies for esophagitis, including viral and ischemic esophagitis, were ruled out.

The patient was enrolled in a serial esophageal dilation program and was referred for concomitant hyperbaric therapy. Her treatment plan involved an initial 30 treatments and 10 additional treatments after any subsequent dilation(s). She underwent 30 treatments (2.4 atmosphere absolute, 115 minutes [U.S. Navy Treatment Table 9]) and had a subsequent upper endoscopy that showed healing of the esophageal ulcer and a benign appearing stenosis measuring 10 cm in length with a 10-mm inner diameter. The stricture was effectively dilated to 12 mm. Based on the favorable response, she underwent serial endoscopic dilations at 2-week intervals for a total of 5 endoscopic procedures and 2 additional postprocedural hyperbaric sessions of 10 treatments. Figure 1 summarizes her treatment plan. Her final upper endoscopy showed an esophageal diameter of 12 mm that was effectively dilated to 15 mm. Figure 2 depicts changes to her esophageal mucosal lining with successive hyperbaric oxygen and serial dilation.

DISCUSSION

The patient we have presented had a radiation-induced stricture that was effectively treated with serial esophageal dilations and adjuvant hyperbaric therapy. Esophageal stricture as the patient developed is evident with scar formation from fibrosis. Acute radiation-induced esophagitis is self-limited and generally does
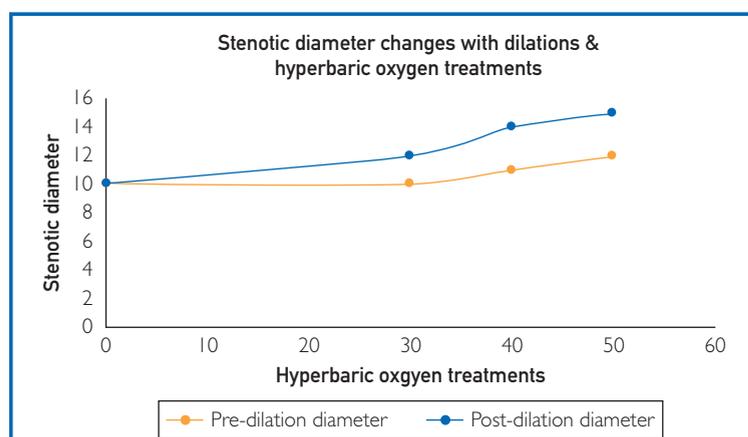

FIGURE 1. Relationship of hyperbaric oxygen therapy and serial esophageal dilation precedures. Esophageal dilations performed at approximately 2-week intervals with hyperbaric oxygen treatments between dilations. Predilation diameter changes were less pronounced, and patient almost lost increase in stenotic diameter between 30th and 40th hyperbaric treatments. Note sustained predilation and postdilation esophageal diameter at the area of stenosis as the patient approaches 14 mm and 50 treatments.

not last more than 4 weeks after cessation of therapy. Radiation-induced stricture develops 3 to 8 months (median: 6 months) after completion of radiation therapy.[14] This patient had stricture 5 months after the completion of her radiation therapy, suggestive of late disease.[15] Radiation-induced strictures can develop in patients receiving limited treatment doses, particularly in the setting of concurrent chemotherapy.[7] Indeed, the literature is scarce on the adverse gastrointestinal effect of concurrent or sequential treatment with novel agents, such as nivolumab and cabozantinib, among patients receiving radiation therapy. A working knowledge of the pathophysiology of radiation-induced, immune-induced, and chemotherapy-related esophageal injury is crucial, as combination regimens are the mainstay of treatment for certain types of metastatic cancer.

Radiation-induced esophagitis is a dose-limiting complication of thoracic external beam radiation. It rarely occurs in patients exposed to 30 Gy or less of radiation. It has been estimated that less than 2% of patients treated with 50 Gy or less develop radiation-induced esophageal stricture, compared with 15% among patients treated with 60 Gy.[16] Our patient received 30 Gy: a routine palliative thoracic radiation dose below Radiation Therapy Oncology Group (RTOG)-recommended mean dose of 34 Gy. Despite this, she progressed from an acute esophagitis RTOG grade I to a grade III in 2 weeks. Predictors of radiation-induced esophagitis are not fully understood, and some patients with relatively small radiation doses have been reported to develop grade I to III esophagitis.[17] Intrinsic and extrinsic factors play different roles in severe radiation-induced esophagitis leading to fibrosis and formation of esophageal stricture. Genetic predisposition resulting from single-nucleotide polymorphisms of transforming growth factor beta 1 (TGF β-1) may present an intrinsic factor contributing to the development of severe radiation esophagitis.[18]

Ionizing radiation causes DNA damage that, in turn, activates proinflammatory cytokines and stress-induced signaling pathways, resulting in endarteritis, breakdown of collagen, and cellular death.[19,20] Pathologic markers include increased mucosal inflammation, epithelial thinning, and denudation.[21]
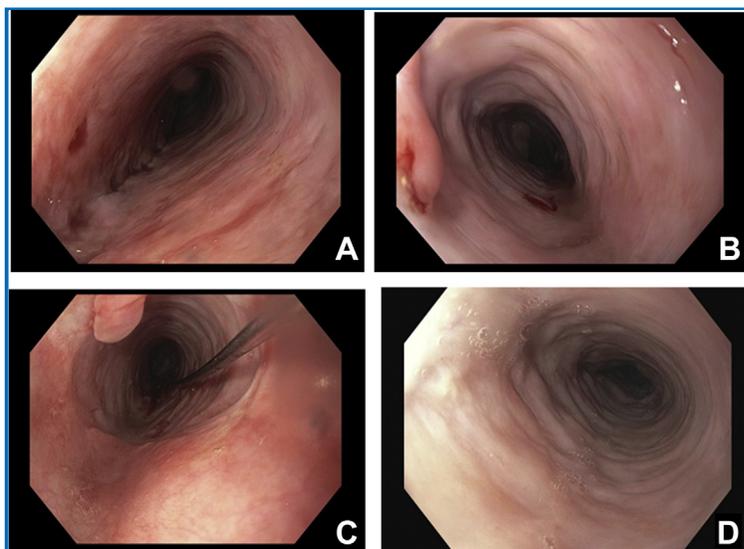

FIGURE 2. Biweekly endoscopic evaluation of lower esophagus. Mucosal appearance during serial EGD done every 2 weeks with interval hyperbaric oxygen treatments. Gradual reduction in erythematous areas and scattered ulcers as seen on the patient's first (A), second (B) and fourth (C) EGD. No appreciable ulcers or mucosal erythema noted on fifth EGD after 50 hyperbaric oxygen treatment and biweekly serial dilations (D). Note, third EGD was few days after the second EGD (not shown here). EGD = esophagogastroduodenoscopy.

These pathologic markers observed in radiation-induced esophagitis are similar to changes noted in caustic esophageal injury, suggesting a common underlying mechanism in the acute phase.[7] One animal study reported reduction in ulcer depths, vascular thrombosis, mortality, and collagen score among rats that had caustic distal esophageal injury among HBO-treated groups compared with the group that did not receive non-HBO.[22] It is biologically plausible to expect similar hyperbaric oxygen treatment benefit(s) to esophageal injury resulting from radiation therapy. Long-term sustained hypoxic state creates a tenuous microenvironment in which metabolic demands exceed supply and accelerate the formation of ulcers from a denuded epithelial lining. Wound healing in previously irradiated mucosa is therefore defective, and subsequent tissue disruption from procedures, such as dilation, is fraught with complications and recurrence and may benefit from adjuvant HBO to support the healing process.[9]

Cabozantinib is a multityrosine kinase inhibitor that acts against several receptors such

as VEGF-2, RET, c-MET, FLT3, and AXL. It inhibits VEGFR-2, HGF-c-MET, and RET angiogenesis pathways. One preclinical study reports inhibition of ongoing angiogenesis with sparing of established vessels.[23] It is not well known how inhibition of angiogenesis from cabozantinib differs from that of radiation. Another animal study that focused on tumor antiangiogenesis reported synergistic effect of concurrent radiation and chemotherapy.[24] Several clinical studies have reported that combining radiation and chemotherapy accelerates radiation-induced esophagitis and development of stricture.[7,25,26]

There is less evidence regarding adverse effects when extracranial palliative radiation is combined with immune checkpoint inhibitors such as anti-PD 1. Anti-PD 1 uncouples the brake-immune signal (PD 1/PD-L1), thereby increasing the baseline T-cell—specific immune response that activates the immune system against cancer cells. This T-cell—mediated action alters the immunologic homeostasis and exhibits autoimmune-like and inflammatory effects on normal tissues, involving B cells, granulocytes, and cytokines. As previously mentioned, concurrent radiation and anti-PD 1 have proinflammatory components, creating a "super-inflammatory" hypoxic field that may accelerate the development of esophagitis and formation of esophageal stricture, among other injuries.

In our patient, the rapid development of severe esophagitis and stricture after palliative thoracic radiation may be due to a process specific to cabozantinib or nivolumab, synergistic effects of concurrent administration of cabozantinib and nivolumab, or an underlying genetic predisposition that accelerated formation of stricture.

OUTCOME
After completing serial dilations to an esophageal luminal diameter of 15 mm and 50 HBO treatments, the patient was ultimately able to tolerate a regular diet with no of evidence dysphagia or odynophagia. The PEG was removed 1 month after her third esophageal dilation. She has remained symptom free and without recurrence for 9 months.

CONCLUSIONS
The successful relief of this patient's symptoms and restoration of regular dietary intake supports the management of radiation-induced esophageal strictures with serial esophageal dilation and adjuvant HBO therapy. Concurrent use of novel chemotherapy agents (nivolumab and/or cabozantinib) may predispose patients to radiation injury regardless of dosage, and sequential therapy as an alternative should be considered. Preclinical studies are required to clarify the pathophysiologic mechanisms whereby the combined use of anti-PD 1 medications and radiation therapy may result in synergistic adverse events. Well-designed randomized trials and/or cohort studies are also needed to elucidate further the role of cabozantinib in accelerating radiation-induced injuries.

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