Osteoradionecrosis of the Sternoclavicular Joint After Laryngopharyngeal Radiation

Rachel Irizarry, MD; Deborah R. Shatzkes, MD; Stephanie Teng, MD; Nikita Kohli, MD; Gady Har-El, MD

**Objectives:** Adequate treatment of laryngopharyngeal malignancy often incorporates radiation therapy. Structures surrounding laryngopharynx exposed to traditional radiation doses are susceptible to posttreatment toxicity. Among poorly understood sequelae is the rare manifestation of sternoclavicular joint (SCJ) osteoradionecrosis (ORN).

**Methods:** Three institutional encounters prompted a comprehensive literature search, generating three published case reports. Systematic extraction and analysis (n = 6) of demographics, cancer history, comorbidities, ORN presentation, imaging, and management established the largest series to investigate this pathology.

**Results:** Patients were males (6), 54 to 70 years old, smokers (4), with Hypertension/dyslipidemia, myocardial infarction/coronary artery disease, second primary (2), diabetes mellitus (1), and myelofibrosis (1). Four underwent total laryngectomy, one primary, three as salvage. Five patients had concurrent chemoradiation (≥70 Gy). All patients presented with swollen, tender neck wounds concerning for persistent/recurrent malignancy. Computed tomography (CT) demonstrated bone erosion (5 of 5) and increased bone scan uptake (2 of 2). All responded to surgical exploration with drainage alone (1), seques-trectomy (2), or bone resection with synovectomy (3). Complete healing took 2 months to 3 years. One unrelated patient death occurred before control of ORN was achieved.

**Discussion:** Given varied patient characteristics, synergistic risk factors exist that alter bone radiation threshold, resulting in irreversible ischemic damage and osteoradionecrosis. Vascular susceptibility and inability to repair may regulate that threshold. Understanding this relationship will facilitate early detection and intervention.

**Conclusion:** Integrating cases of sternoclavicular joint ORN promotes awareness of atypical laryngopharyngeal radiation complications, elucidates contributing factors, educates physicians on presentation and management, and provides a platform for prospective investigation.

**Key Words:** Osteoradionecrosis, osteonecrosis, head and neck radiation, sternoclavicular joint.

**Level of Evidence:** 4

INTRODUCTION

Radiation therapy is an essential component of effective head and neck cancer (HNC) treatment. Approximately 80% of all HNC patients receive radiation therapy (RT) at least once during their disease course and are therefore at risk of developing post-treatment toxicity. Healthy structures abutting the radiation field are particularly susceptible to these toxicities. Manifestations of these toxicities vary in both onset and severity. Intolerance of toxicity can limit the delivery of effective radiation doses and result in long-term morbidity impairing laryngopharyngeal function and quality of life. Despite the large population of HNC patients experiencing these complications, insufficient data exists to accurately characterize patient specific toxicity risk and subsequent progression.

Among poorly understood sequelae of HNC radiation is the infrequently encountered manifestation of sternoclavicular joint (SCJ) osteoradionecrosis (ORN). Although it is an acknowledged complication of chest wall radiation for breast or lung cancer, it is unexpected following laryngopharyngeal radiation. Yet at our institution we encountered three patients diagnosed with ORN of the SCJ following HNC treatment, prompting us to investigate this occurrence in the literature. Unexpectedly, this pathology was mentioned as an outlier in several studies examining adverse effects of radiation therapy. Detailed findings were presented in three case reports, each perceived as isolated events. Given these findings, we felt that consolidation of all cases of the disease process and aggregation of patient data was essential. The aim of this review is to increase awareness among professionals who treat or diagnose head and neck cancer, educate physicians on presentation and management of SCJ ORN, and elucidate potential influential factors.

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Institution where work was performed: Lenox Hill Hospital and The New York Head and Neck Institute, New York, New York, U.S.A.

Editor’s Note: This Manuscript was accepted for publication on May 7, 2018.

Presented at the COSM Spring Meeting, American Laryngological Society, National Harbor, Maryland, U.S.A., April 18–20, 2018.

The authors have no funding, financial relationships, or conflicts of interest to disclose.

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MATERIALS AND METHODS
Following encounters with three patients at our institution who developed SCJ ORN after laryngopharyngeal radiation therapy, an expansive literature search on this complication was performed. Search terms included osteoradionecrosis head and neck, radiation osteonecrosis head and neck ± clavicle ± sternum ± sternoclavicular joint, and complications head and neck radiation. Three published case studies were found with sufficient clinical detail to incorporate into our data analysis. Inclusion criteria included laryngopharyngeal radiation treatment, sternoclavicular joint ORN pathological diagnosis, and description of presentation and management techniques. Data extracted from each case included patient demographics, cancer staging, site, detailed treatment course (radiation administered, ± surgery performed, and ± chemotherapy course administered), comorbidities, social history (when provided), ORN presentation, imaging performed, management technique, operative intervention, pathological findings, and outcome.

RESULTS
Patient demographics (Table I) and cancer site, stage, and treatment course (Table II) were analyzed for possible contributing risk factors. Radiological studies were performed, and comparison of findings were detailed (Table III). Management, surgical intervention, and outcome were summarized (Table IV).

Demographics
Patients were all males (6); 54 to 70 years old; smokers (4); with hypertension/dyslipidemia (HTN/DLD) (5), myocardial infarction/coronary artery disease (MI/CAD), second primary (2), diabetes mellitus (DM) (1), and myelofibrosis (1). Of the four confirmed smokers, all had established coexisting HTN and DLD. Two out of the six patients had prior cardiac events. Ischemic events requiring transfusion occurred in three out of six patients approaching diagnosis and treatment of osteoradionecrosis. One patient had moderately controlled type 1 diabetes mellitus, and two of the patients had second primaries requiring treatment.

Diagnostic and Treatment Details
Primary cancers were distributed among supraglottic (1), pyriform sinus (2), base of tongue (1), and glottic (2). Five out of six patients had aggressive disease characterized by extensive nodal involvement, recurrence, or disease progression to advanced stage despite initial treatment. Staging on presentation included stage IV disease (3 patients), stage III disease (1 patient), stage II disease (1 patient), and stage 0 (Cis). Three patients presented with nodal involvement. The two early stage patients (stage II and carcinoma in-situ) both progressed to stage IV despite treatment. Only the stage III patient remained disease-free after initial treatment. Two patients were definitively treated with concurrent chemotherapy and radiation, and both required tracheotomy placement. Four patients required total laryngectomy, one as primary treatment and the other three as salvage therapy. Five out of six patients received 7,000 Gray (Gy) to primary site in 35 to 39 fractions, with the outlier receiving adjuvant therapy of 50 Gy with tumor and mediastinum boosted with 30 Gy. Five out of six patients received concurrent chemotherapy and radiation (≥ 70 Gy).

Presentation
Sternoclavicular ORN presented as a nonhealing peristomal wound (Fig. 1) in 100% of patients. Associated findings included cellulitic chest wall changes (5 of 6), drainage (4 of 6), and pain (5 of 6). Imaging performed included CT (5 of 6), bone scan (2 of 6) and positron emission tomography (PET) scan (1 of 6), which was consistently insufficient to differentiate osteomyelitis (OM). ORN, or recurrence (Fig. 2). Findings included bony necrosis with surrounding inflammatory changes (6 of 6), cellulitic chest wall changes (5 of 6), and drainage (4 of 6).

TABLE I.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age at Diagnosis</th>
<th>Comorbidities</th>
<th>SH</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jabourdin 1988</td>
<td>64 M</td>
<td>CAD, MI, a-fib, HTN, gastric ulcer requiring transfusion</td>
<td>40 pack year, alcohol abuse</td>
<td>Digoxin, HCTZ</td>
</tr>
<tr>
<td>Syed 2007</td>
<td>65 M</td>
<td>Gastric ulcer requiring transfusion, carotid blow-out</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Gehani 2013</td>
<td>54 M</td>
<td>DM</td>
<td>Denies</td>
<td>Unknown</td>
</tr>
<tr>
<td>SG</td>
<td>69 M</td>
<td>HTN, CAD, DLD, BPH, glaucoma, colon ca</td>
<td>1.5 PPD x 20 years, former alcoholic</td>
<td>Amlodipine, plavix, ASA, losartan metoprolol, atorvastatin, doxazosin, tamsulosin, latanoprost</td>
</tr>
<tr>
<td>PP</td>
<td>68 M</td>
<td>Polycythemia vera, melanoma, HTN, HLD, bronchial artery bleed requiring transfusion</td>
<td>Alcohol tobacco</td>
<td>Hydroxyurea, liptor, ASA, omeprazole</td>
</tr>
<tr>
<td>AZ</td>
<td>70 M</td>
<td>HTN</td>
<td>40 pack year history of smoking no alcohol use</td>
<td>HCTZ</td>
</tr>
</tbody>
</table>

a-fib = atrial fibrillation; ASA = aspirin; BPH = benign prostatic hyperplasia; ca = cancer; CAD = coronary artery disease; DM = type 1 diabetes mellitus; HCTZ = hydrochlorothiazide; HTN = hypertension; MI = myocardial infarction; PPD = pack per day. Note: SG, PP, and AZ are unique identifiers of patients cared for in our facility.

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joint effusion with widening of SCJ (2 of 6), and bony erosion (3 of 6). Definitive diagnosis required pathologic examination. All specimens were negative for malignancy and consistent with osteoradionecrosis. Adequate therapy required surgical debridement (6 of 6), intravenous antibiotics (IV) (6 of 6), and prolonged wound care (6 of 6). Complete response required surgical exploration with drainage alone (1), sequestrectomy (2), or bone resection with synovectomy (3).

**DISCUSSION**

Basic pathophysiology of radiation toxicity development is widely understood and accepted. Because radiation exposure restricts tumor cell reproduction, it also induces cell death (acute toxicity) and alteration of cell signaling pathways (late toxicity) in healthy tissue cells. Tissues are unique in their response and recovery pattern, creating clinical profiles of toxicity and expected reactions unique to each organ system and easily accessible in radiation oncology literature. Bone is believed to be a relatively radioresistant organ system. Initial data suggested that mature bone could tolerate up to 65 Gy without significant morbidity. More recent studies have identified factors that lower this threshold based on volume exposed. Bone exposed to fractionated doses of > 60 to 65 Gy have a 2% to 20% rate of ORN. Incidence varies based on volume of exposure, 5-FU-5-fluorouracil; ALT = anterolateral thigh; b/l = bilateral; CCRT = concurrent chemotherapy & radiation; Cis = carcinoma in situ; Gy = Gray; frac = fractions; N = No; ND = neck dissection; OP = oropharynx; RND = right neck dissection; RT = radiation therapy; TL = totally laryngectomy; TLM = trans-oral laser microsurgery; tx = treatment; Y = Yes. Note: SG, PP, and AZ are unique identifiers of patients cared for in our facility.

<table>
<thead>
<tr>
<th>Case</th>
<th>Primary Stage</th>
<th>Tx</th>
<th>Recurrence</th>
<th>Surgery</th>
<th>Chemo</th>
<th>Radiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jabourdian 1988</td>
<td>Hypopharynx</td>
<td>T3N0M0</td>
<td>N</td>
<td>No, post-tx tracheostomy</td>
<td>5-FU/cisplatin, 3 courses</td>
<td>70 Gy/38 frac bilateral necks tx 50 Gy to clavicle</td>
</tr>
<tr>
<td>Syed 2007</td>
<td>Supraglottic</td>
<td>T4aN2aM0</td>
<td>N</td>
<td>TL RND</td>
<td>N</td>
<td>56 Gy/26 frac tumor site/medialstium boosted 30 Gy/5 fractions</td>
</tr>
<tr>
<td>Gehani 2013</td>
<td>OP (tongue base)</td>
<td>T4aN2cM0</td>
<td>N</td>
<td>N, pre-tx tracheostomy</td>
<td>5-FU/cisplatin, 2 cycles</td>
<td>70.2 Gy to gross disease, 50.4 to at risk areas/39 fractions</td>
</tr>
<tr>
<td>SG</td>
<td>Hypopharynx (second primary-color)</td>
<td>T2N2bM0</td>
<td>Y</td>
<td>TL, partial pharyngectomy, b/l ND, ALT flap reconstruction</td>
<td>Primary: CCRT 3 weekly cisplatin recurrence; weekly cetuximab</td>
<td>Primary: 70 Gy/35 frac, b/l neck Recurrence: 50 Gy/25 frac ×6</td>
</tr>
<tr>
<td>PP</td>
<td>Glottic (second primary melanoma)</td>
<td>Cis</td>
<td>Y</td>
<td>Primary: TLM × 5 Recurrence: TL</td>
<td>Limited chemo</td>
<td>Definitive RT</td>
</tr>
<tr>
<td>AZ</td>
<td>Glottic</td>
<td>T2N0M0</td>
<td>Y</td>
<td>Primary: none Recurrence: TL with b/l ND</td>
<td>5-FU/cisplatin</td>
<td>70 Gy to primary site/38 frac</td>
</tr>
</tbody>
</table>

5-FU-5-fluorouracil; ALT = anterolateral thigh; b/l = bilateral; CCRT = concurrent chemotherapy & radiation; Cis = carcinoma in situ; Gy = Gray; frac = fractions; N = No; ND = neck dissection; OP = oropharynx; RND = right neck dissection; RT = radiation therapy; TL = totally laryngectomy; TLM = trans-oral laser microsurgery; tx = treatment; Y = Yes. Note: SG, PP, and AZ are unique identifiers of patients cared for in our facility.
TABLE IV. Presentation, Management, and Outcome of Sternoclavicular Osteoradionecrosis.

<table>
<thead>
<tr>
<th>Case</th>
<th>Presenting Sx</th>
<th>Time From Completion of Therapy</th>
<th>Treatment</th>
<th>Resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jabourdian 1988</td>
<td>Peristomal cellulitis, movement restriction, SCJ tenderness</td>
<td>2 years</td>
<td>IV antibiotics, sequestrectomy with synovectomy, right medial claviculectomy to close clavicular-tracheal fistula, tracheostomy, wound care</td>
<td>1 year, decannulated</td>
</tr>
<tr>
<td>Syed 2007</td>
<td>Nonhealing ulcer, hemorrhage</td>
<td>14 years</td>
<td>IV antibiotics operative drainage, sequestrectomy, pec major myocutaneous flap</td>
<td>2 months, healed laryngectomy stoma</td>
</tr>
<tr>
<td>Gehani 2013</td>
<td>Persistent tracheocutaneous fistula, purulent drainage</td>
<td>8 months</td>
<td>Primary: IV antibiotics, conservative drainage, HBO Secondary: sequestrectomy with complete synovectomy, b/l partial claviculectomies, partial sternectomy, pectoralis myocutaneous flap, permanent tracheostomy</td>
<td>3 years, permanent tracheostomy</td>
</tr>
<tr>
<td>SG</td>
<td>Intermittent peristomal and chest wounds with cellulitic changes</td>
<td>7 years/during second treatment</td>
<td>Primary: complete synovectomy and limited sequestrectomy, vigilant wound care with dakins and packing changes, IV antibiotics</td>
<td>6 months</td>
</tr>
<tr>
<td>PP</td>
<td>Tracheoesophageal fistula, chest wall abscess</td>
<td>3 months</td>
<td>Primary: IV antibiotics, bedside debridement, conservative drainage Secondary: operative drainage, aggressive wound care</td>
<td>Patient expired</td>
</tr>
<tr>
<td>AZ</td>
<td>Cellulitic changes of chest wall</td>
<td>2 months</td>
<td>IV antibiotics, surgical debridement, sequestrectomy, prolonged 6 months wound care</td>
<td>6 months</td>
</tr>
</tbody>
</table>

HBO = hyperbaric oxygen; IV = intravenous; SCJ = sternoclavicular joint. Note: SG, PP, and AZ are unique identifiers of patients cared for in our facility.

Fig. 1. Physical exam findings characteristic of SCJ ORN. As suggested by our review, a typical feature of SCJ ORN is the presence of a non-healing wound around the joint site in close proximity to an existing stoma. This is often associated with drainage, tenderness, and surrounding cellulitic changes that are challenging to distinguish from underlying recurrent malignancy. Above are the stomal wounds encountered in two patients treated at our facility, both consistent with the typical presentation (A) Patient SG (B) Patient PP. Note: SG, PP, and AZ are unique identifiers of patients cared for in our facility. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]
which is determined by both target size, dose administered, and technique of radiation administration. HNC patients are at increased risk for ORN given the typical radiation regimen of 60 to 70 Gy and the close proximity of adjacent critical structures.\textsuperscript{1,2,9,10} The highest rates of HNC ORN have been documented in the oral cavity (15\%), documented incidence of ORN in HNC of the laryngopharynx is about 4.1\%. Rates are significantly influenced by primary tumor stage (T4 or not), RT treatment technique (intensity modulated radiation therapy/volumetric modulated arc radiotherapy or not), radiation dose (70 Gy or less), and age (greater than years or not)\textsuperscript{2} findings that are seen consistently across multiple studies.\textsuperscript{1,2,9,10} Our study reflected similar risk factors in that all of the patients, except one presented with or progressed to T4 disease, were exposed to 70 Gy, and 83\% of patients or greater at time of ORN diagnosis. Yet, our data represents the spectrum of staging at initial diagnosis, with 83\% progressing to stage IV disease despite appropriate early stage treatment. This intrinsic tumoral factor likely contributes to a more aggressive clinical course and, once identified, may serve as a target to identify patients that could benefit from earlier aggressive therapy.

Fig. 2. Osteoradionecrosis presentation on imaging. Imaging performed on patients displayed in Figure 1. CT findings (A,C) demonstrate erosion, effusion, and widening of sternoclavicular joint. PET scan findings (B) and gallium bone scan findings (D) show hypermetabolic activity consistent with OM, ORN, or malignancy. Patient SG (a) CT chest noncontrast enhanced; (b) PET CT Patient PP; (c) CT chest with contrast; (d) gallium scan. \textit{CT} = computed tomography; \textit{OM} = osteomyelitis; \textit{ORN} = osteoradionecrosis; \textit{PET} = positron emission tomography. Note: SG, PP, and AZ are unique identifiers of patients cared for in our facility. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]
typically presenting 1 to 2 years after treatment.\textsuperscript{10–12} One theory of development stems from radiation-induced dysregulation of fibroblast activity. These radiation-induced fibroblasts create an environment of vascular fibrosis and thrombosis, resulting in tissue ischemia and bone that is hypoxic, hypocellular, and hypovascular.\textsuperscript{1} The resulting bone becomes necrotic and prone to both infection and traumatic breakdown. Our study supports this theory, in that all patients demonstrated impaired impaired blood delivery mechanisms. Etiology of ischemia was secondary to acute blood loss requiring transfusion or underlying microvascular disease both of which could potentially augment hypovascular effects of radiation. Furthermore, all our patients required formation of a stoma in close proximity to the SCJ, a surgical intervention that induces trauma and necessitates wound healing. The theory of an underlying ischemic process is further supported by the impaired stomal healing uniformly seen among our patients.

Analogous to mandibular ORN, the diagnosis of SCJ ORN requires a combination of diagnostic tools. As evidenced by our study, presentation often involves cellular changes, with pain and a nonhealing wound. Drainage or exposed bone may also be present. Imaging performed often begins with a contrast enhanced CT but may be supplemented by PET or bone scan. Findings of bony necrosis are universal but insufficient to differentiate between OM, ORN, and recurrent malignancy. Biopsy is essential to rule out recurrence and confirm ORN diagnosis. Treatment involves close monitoring, meticulous wound care, antibiotic coverage, and escalated debridement, as indicated. A spectrum of surgical interventions should be considered based on patient response starting with simple bedside debridement and terminating at bone resection with complete synovectomy. Grossly necrotic bone should be resected to healthy tissue with preplanned reconstruction and consultation that includes appropriate specialty services. Mycoticaneous flaps may be required for sinus tracts, fistulas, or large chest wall defects. Emphasis should be placed on quality-of-life consideration prior to each intervention. Conservative approaches should be performed when appropriate with vigilant escalation for inadequate response to therapy.

\section*{CONCLUSION}

Although abundant and unified data on mandibular ORN exists, similar data is lacking for ORN of the SCJ. By aggregating existing data, we have provided an opportunity to increase awareness of the disease process and provide a guideline for approaching treatment. Informed providers are essential to facilitate and expedite the diagnosis, clarify prevalence, initiate appropriate workup and management, and most importantly, enhance quality of life for those affected.

\section*{Acknowledgment}

We would like to thank all members of the healthcare team who assisted in the care of these patients and whose diligence enabled completion of this project.

\section*{BIBLIOGRAPHY}