

## Neurologic late effects associated with radiologic evidence of vertebral osteoradionecrosis after salvage laryngectomy: A syndrome associated with survivors of laryngeal and hypopharyngeal cancer

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Accepted 17 October 2015

Published online 15 April 2016 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/hed.24348

**ABSTRACT:** *Background.* Delayed nonspecific posterior neck pain after pharyngeal instrumentation can be associated with a syndrome of rapidly progressive neurologic embarrassment. We present this cohort to help define the syndrome and aid in early detection.

*Methods.* We conducted a retrospective case series of 6 patients presenting from 2003 to 2012 with a history of laryngeal or hypopharyngeal squamous cell carcinoma (SCC) who underwent radiotherapy (RT) or chemoradiotherapy (CRT) followed by salvage laryngectomy.

*Results.* Posterior neck and upper back pain developed a mean of 27.5 days after instrumentation of the pharynx (reconstruction after

laryngectomy or pharyngeal dilation). Myelopathy developed an average of 21.5 days after the onset of posterior neck pain. Five patients required urgent decompression. Three patients developed quadriplegia. The disease-specific mortality was 50%.

*Conclusion.* There is a syndrome of late neurological effects after RT, salvage surgery, and pharyngeal instrumentation that is associated with high morbidity and mortality. © 2016 Wiley Periodicals, Inc. *Head Neck* 38: 1187–1193, 2016

**KEY WORDS:** late effects, head and neck cancer, myelopathy, osteoradionecrosis, salvage laryngectomy

### INTRODUCTION

Since the Veterans Affairs laryngeal cancer study was published in 1991, there have been an increasing number of patients with stage III and IV laryngeal and hypopharyngeal squamous cell carcinoma (SCC) being treated with chemoradiotherapy (CRT). The major advantage of this treatment approach is preservation of the larynx in two thirds of the surviving patients during the first 5 years posttreatment. Preservation of the larynx is a clear advantage, but for some patients there are unpredictable late effects.<sup>1</sup> Although radiotherapy (RT) and CRT provide a chance for organ preservation, treatment has deleterious effects on adjacent normal tissue, as it induces a hypoxic, hypocellular, and hypovascular environment.<sup>2</sup> The tissue effects are the most pronounced for patients who undergo primary RT or CRT and require salvage surgery for persistent or recurrent disease. This study attempts to describe the syndrome of subtle posterior neck and upper back pain in patients after surgical instrumentation of their pharynx with a history of RT who progress to myelopathy with radiologic evidence of spinal

epidural thickening and loss of fat signal in the marrow space of the cervical vertebrae compatible with cervical vertebral osteoradionecrosis (ORN).

### MATERIALS AND METHODS

#### Study design

A retrospective case series of 6 patients who developed a syndrome of nonspecific posterior neck pain localized to the vertebrae with neurologic symptoms of myelopathy and radiologic evidence of vertebral ORN was conducted. To evaluate the characteristics of this syndrome, a retrospective chart review was performed at the University of Michigan for patients presenting between 2003 and 2012.

#### Eligibility criteria

Patients were eligible for inclusion in the cohort if they had a history of SCC of the larynx or hypopharynx treated with curative RT with or without chemotherapy and subsequently developed a syndrome of subtle pain in the posterior neck and upper back 1 to 8 weeks after instrumentation of the pharynx associated with symptoms of myelopathy and radiologic evidence of spinal epidural thickening and loss of fat in the marrow space of the cervical vertebrae compatible with cervical vertebral ORN.

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**TABLE 1. Patient characteristics at laryngectomy.**

| Characteristics                      | No. of patients  |
|--------------------------------------|------------------|
| Sex                                  |                  |
| Male                                 | 50% (3/6)        |
| Female                               | 50% (3/6)        |
| Age, y, mean (range)                 | 60.6 (55–66)     |
| BMI, mean (range)                    | 23.2 (17.8–33.5) |
| TSH, mean (range)                    | 2.86 (0.47–5.5)* |
| Albumin, mean (range)                | 3.45 (1.3–4.3)†  |
| Diabetes                             | 17% (1/6)        |
| Tobacco use                          |                  |
| Current                              | 67% (4/6)        |
| Former                               | 33% (2/6)        |
| Never                                | –                |
| Alcohol use                          |                  |
| Current                              | 17% (1/6)        |
| Former                               | 50% (3/6)        |
| Never                                | 33% (2/6)        |
| Subsite                              |                  |
| Supraglottis                         | 17% (1/6)        |
| Glottis                              | 33% (2/6)        |
| Subglottis                           | 17% (1/6)        |
| Piriform sinus                       | 33% (2/6)        |
| T classification                     |                  |
| T1                                   | –                |
| T2                                   | 50% (3/6)        |
| T3                                   | 33% (2/6)        |
| T4                                   | 17% (1/6)        |
| N classification                     |                  |
| N0                                   | 67% (4/6)        |
| N1                                   | –                |
| N2a                                  | 17% (1/6)        |
| N2b                                  | 17% (1/6)        |
| N2c                                  | –                |
| N3                                   | –                |
| Radiation dose, mean (range)         | 71 Gy (68–75 Gy) |
| Indication for laryngectomy          |                  |
| Recurrence                           | 83% (5/6)        |
| Chondroradionecrosis                 | 17% (1/6)        |
| Surgical defect                      |                  |
| Total laryngectomy                   | 67% (4/6)        |
| Total laryngopharyngectomy           | 33% (2/6)        |
| Cricopharyngeal myotomy              | 100% (6/6)       |
| Tracheoesophageal puncture           | 100% (6/6)       |
| Autologous tissue for reconstruction |                  |
| Radial forearm                       | 50% (3/6)        |
| Anterolateral thigh                  | 33% (2/6)        |
| Lateral arm                          | 17% (1/6)        |

Abbreviations: BMI, body mass index; TSH, thyroid-stimulating hormone; MD, metastatic disease.

\* Laboratory tests not ordered preoperatively for 1 patient.

† Laboratory tests not ordered preoperatively for 2 patient.

**Initial presentation and treatment**

Patient demographics and oncologic treatment are shown in Tables 1 and 2. When initially diagnosed with SCC of the larynx or hypopharynx, half of the patients presented with stage II disease and the other half presented with stage IV disease. Of the 5 patients who underwent chemotherapy, 2 patients received carboplatin alone, 1 received carboplatin and 5-fluorouracil, 1 received carboplatin and paclitaxel, and 1 received 5-fluorouracil, docetaxel, and hydroxyurea. The remaining patient received amifostine. The average radiation dose

delivered to the primary site was 71 Gy (range, 68–75 Gy). One patient received b.i.d. fractionation and had 5 weeks of treatment. The remaining patients were treated with daily fractionation over 7 weeks. Two patients received RT at the University of Michigan with the remainder being treated at other institutions. Radiation fields were not available in 2 patients treated at outside institutions. The mean and maximum doses to the cervical vertebral bodies (C4–C6) were 54.4 Gy and 69.8 Gy, respectively.

**Salvage surgery**

The mean interval between RT and salvage surgery was 25.9 months (range, 11.6–70.8 months). Four of 6 patients (67%) underwent total laryngectomy and 2 of 6 patients (33%) underwent a total laryngopharyngectomy. All patients underwent autogenous tissue transplantation for reconstruction and cricopharyngeal myotomy for voicing with the immediate placement of a nasogastric tube for nutrition. All patients underwent delayed tracheal-esophageal puncture.

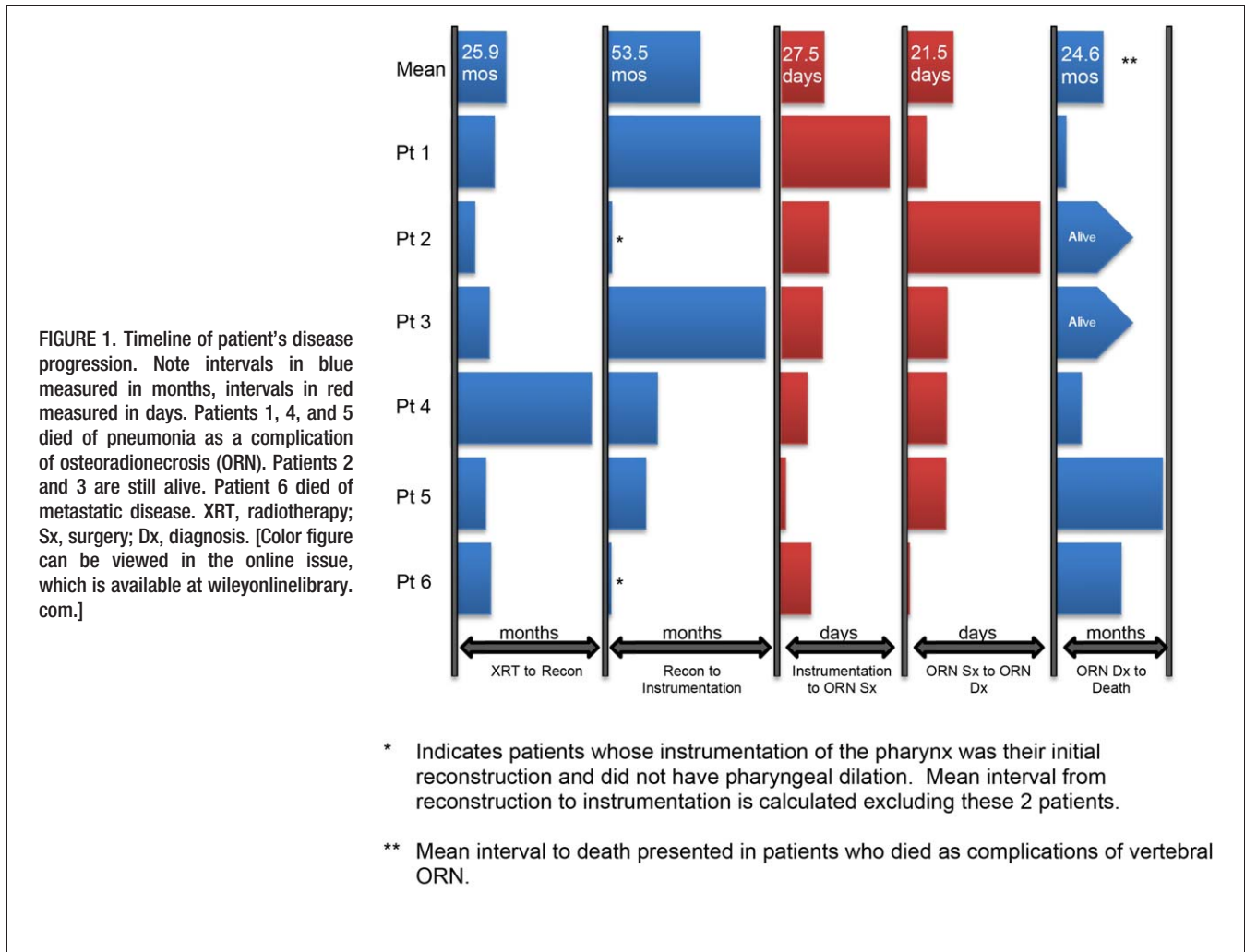
**Statistical analysis**

Variables under study included age, sex, tumor classification, timing of RT, chemotherapeutic regimen, indication for salvage surgery, surgical defect, and reconstructive approach. Variables specific to the syndrome were collected, including instrumentation of the pharynx, presenting symptoms, interval to diagnosis, microbiological culture, alcohol use, tobacco use, body mass index (BMI), thyroid-stimulating hormone (TSH), and albumin. Specific outcomes of interest included neurologic disability and recovery after treatment. The date of instrumentation of the pharynx was defined as the most recent pharyngeal dilation (in the case of 4 patients) or reconstruction of the pharynx after surgical salvage (in the case of 2 patients) before the development of the syndrome. The date of symptom onset was defined as the first date that patients experienced neck or high back pain. The date of radiologic evidence of vertebral ORN diagnosis was the date that cross-sectional imaging was obtained showing spinal epidural thickening and loss of fat in the marrow space of the cervical vertebrae. Microbial culture data were available in all patients. Antibiotic regimen was tabulated. Disease-specific survival was determined from the date of imaging showing loss of fat in the marrow space of the vertebral body. Univariate statistics were calculated, including mean and range. This study received University of Michigan Institutional Review Board approval.

**TABLE 2. Patient characteristics at vertebral osteoradionecrosis diagnosis.**

| Characteristics       | No. of patients  |
|-----------------------|------------------|
| Age, y, mean (range)  | 63.7 (56.8–73.0) |
| BMI, mean (range)     | 23.6 (17.6–30.8) |
| TSH, mean (range)     | 8.36 (1.5–13.75) |
| Albumin, mean (range) | 3.5 (3.0–4.2)    |

Abbreviations: BMI, body mass index; TSH, thyroid-stimulating hormone.



## RESULTS

### Summary of the syndrome

The syndrome includes nonspecific symptoms of posterior neck pain localized to the vertebrae with neurologic symptoms of myelopathy and radiologic evidence of cervical dural thickening and loss of fat in the marrow space of the cervical vertebrae compatible with a radiologic diagnosis of vertebral ORN that is culture-positive for salivary organisms. This developed in 6 patients with a history of SCC of the larynx or hypopharynx treated with RT with or without chemotherapy followed by salvage laryngectomy. Symptoms of the syndrome developed a mean of 27.5 days after instrumentation of the pharynx (reconstruction after laryngectomy or pharyngeal dilation). Neurologic symptoms of myelopathy developed an average of 21.5 days after symptom onset, which prompted cross-sectional imaging. Most patients required surgical decompression and stabilization of the cervical spine. All patients underwent a prolonged course of broad-spectrum antibiotics. Disease-specific mortality was 50% (see Figure 1).

### Instrumentation of the pharynx

In this cohort, 4 of 6 patients (67%) presented with the syndrome after dilation for pharyngeal stenosis and 2 of 6

patients (33%) presented after developing either a fistula or dehiscence of the closure while healing from pharyngeal reconstruction after salvage laryngectomy. For those undergoing dilation, the mean interval between salvage laryngectomy with pharyngeal reconstruction and the inciting instrumentation of the pharynx was 53.5 months (range, 20.9–83.9 months). There were no frank perforations during the dilation of any patient. For the 6 patients, the mean interval from instrumentation (dilation or reconstruction) of the pharynx to the development of symptoms was 27.5 days (range, 9–56 days).

### Presenting symptoms and signs

All patients initially presented with posterior neck pain localized to the vertebrae and 2 of 6 patients (33%) reported a concurrent headache. The mean interval between the onset of neck and back pain and subsequent development of myelopathy was 21.5 days (range, 1–65 days). Symptoms and signs of myelopathy included isolated bowel incontinence (1 of 6 patients; 17%), upper extremity weakness and paresthesias (1 of 6 patients; 17%), lower extremity weakness and paresthesias (1 of 6 patients; 17%), hemiplegia (Brown–Sequard; 1 of 6 patients; 17%), or quadriplegia (2 of 6 patients; 33%). Fifty percent of patients were febrile at presentation and

TABLE 3. Presenting symptoms and signs.

| Signs and symptoms                 | No. of patients         |
|------------------------------------|-------------------------|
| Headache                           | 33% (2/6)               |
| Posterior neck or upper back pain  | 100% (6/6)              |
| Upper extremity weakness/numbness  | 17% (1/6)               |
| Lower extremity weakness/numbness  | 17% (1/6)               |
| Isolated urinary/bowel dysfunction | 17% (1/6)               |
| Hemiplegia                         | 17% (1/6)               |
| Quadriplegia                       | 33% (2/6)               |
| Fever                              | 50% (3/6)               |
| Tachycardia                        | 67% (4/6)               |
| Hypotension                        | 33% (2/6)               |
| Hyponatremia                       | 83% (5/6)               |
| Leukocytosis                       | 83% (5/6)               |
| Elevated ESR                       | 100% (5/5)*             |
| Elevated CRP                       | 100% (3/3) <sup>†</sup> |

Abbreviations: ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

\*Laboratory tests not ordered at presentation for 1 patient.

<sup>†</sup>Laboratory tests not ordered at presentation for 3 patients.

all but one had a leukocytosis. Mean white blood cell count was 13.7 (range, 6.1–17.9). Four of 6 patients were tachycardic at presentation with 2 of 6 being hypotensive. Eighty-three percent of the patients (5 of 6) were hyponatremic at the time of diagnosis. The erythrocyte sedimentation rate (ESR; mean, 83; range, 37–122) and C-reactive protein (CRP; mean, 8.3; range, 1.8–15.6) were elevated in all patients (Table 3). Cross-sectional imaging showed loss of fat signal in the marrow space of the cervical vertebrae, myelitis of the adjacent spinal

cord, and thickening and enhancement of the dura. Five of 6 patients (83%) had evidence of an epidural fluid collection. The epidural fluid collection was a very subtle finding on CT and seemed to be a thickening of the epidural tissues. Five of 6 patients (83%) required an MRI scan (see Figure 2).

**Acute neurosurgical management**

All but 1 patient required emergent decompression by neurosurgery within 24 hours of diagnosis. The remaining patient had isolated bowel and bladder incontinence with hyperreflexia in the lower extremities without evidence of an epidural fluid collection. In the remaining 5 patients, 1 underwent laminectomy with drainage of the epidural abscess, 1 underwent laminectomy with posterior fusion, and 3 underwent laminectomy, corpectomy with anterior and posterior fusion. Bone and tissue biopsies were taken in 3 of the 6 patients (50%), all of whom showed bone and soft tissue necrosis and fibrosis, consistent with vertebral ORN. Biopsies were not taken in the remaining 3 patients. Three patients required more than 1 operation with 1 patient with the syndrome undergoing 10 operations, including the creation of a diverting pharyngostoma because of recurrent infections. This patient developed a meningocele and cerebrospinal fluid leak leading to recurrent meningitis requiring a deltopectoral flap, pectoralis flap, and tensor fascia lata graft for closure.

**Microbiology**

Tissue cultures were obtained from all patients. Open cultures were obtained from the bone (1 of 6) and the

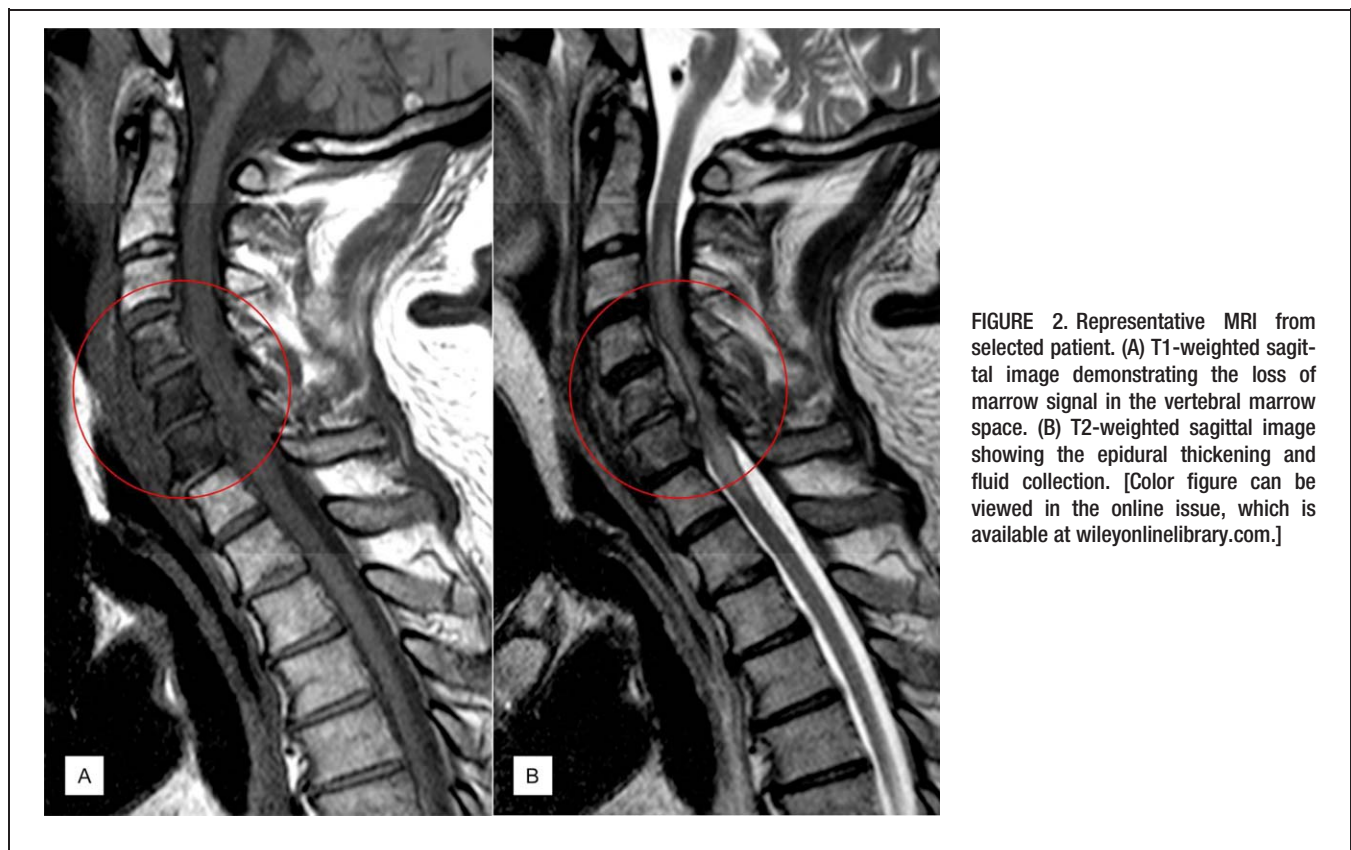


FIGURE 2. Representative MRI from selected patient. (A) T1-weighted sagittal image demonstrating the loss of marrow signal in the vertebral marrow space. (B) T2-weighted sagittal image showing the epidural thickening and fluid collection. [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]



**TABLE 4.** Proposed protocol for the diagnosis and treatment of late neurological effects associated with radiologic evidence of vertebral osteoradionecrosis.

| Vertebral ORN protocol  |
|---|
| <ol style="list-style-type: none"> <li>1. Maintain a high index of suspicion in patients who present with new posterior neck, or back pain with or without headache in the context of recent instrumentation of the pharynx or mucosal disruption.</li> <li>2. Obtain vital signs, including temperature, blood pressure, and heart rate as well as laboratory tests, including a basic metabolic panel to assess for hyponatremia, complete blood count with differential to assess for leukocytosis along with ESR and CRP.</li> <li>3. Because of immediate availability of CT with contrast, obtain a screening CT.</li> <li>4. Confirm the diagnosis with MRI if questions persist.</li> <li>5. Obtain early neurosurgery consultation at the same time as imaging is requested for possible urgent stabilization, abscess drainage, and cultures. Use a posterior approach for the drainage.</li> <li>6. Promptly begin empiric broad-spectrum antibiotics with consultation from the infectious disease department.</li> <li>7. Admit the patient to the hospital for frequent neurologic examinations.</li> <li>8. Tailor antibiotics to culture results, if available.</li> <li>9. Perform pharyngeal diversion to prevent further salivary soiling of vertebrae, if necessary.</li> </ol> |

Abbreviations: ORN, osteoradionecrosis; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

epidural space (4 of 6) in 5 patients and a percutaneous culture from the disc space was obtained from the remaining patient. All but 1 patient had a polymicrobial infection and all organisms cultured were consistent with contamination from the pharynx. Again, it is important to note that in 4 of 6 patients there was no associated disruption of the visceral space. Four of 6 patients grew Streptococcal species in their cultures. Isolated organisms included *Streptococcus viridans*, group B streptococcus, *Streptococcus milleri*, hemophilus influenza, *Klebsiella*, methicillin-sensitive and methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Enterococcus*, *Proteus vulgaris*, *Saccharomyces cerevisiae*, *Candida*, *Citrobacter freundii*, *Fusobacterium nucleatum*, and anaerobes, not otherwise specified. Patients were treated with broad-spectrum i.v. antibiotics.

### Other risk factors

At the time patients presented with this syndrome, there were no current alcohol users and only 1 of 6 patients (17%) was a current smoker. BMI did not seem to infer extra risk for vertebral ORN as only 1 patient (17%) was underweight at the time of salvage laryngectomy and 1 patient was underweight at the time of developing neurological sequela. All but 2 patients had an albumin of 3.5 or greater at the time of ORN diagnosis. All patients were euthyroid (mean TSH, 2.86; range, 0.47–5.5) at the time of salvage laryngectomy, however, 50% of the patients (3 of 6) were found to be hypothyroid at the time of developing neurological sequela (mean, 8.36; range, 1.5–13.75).

### Outcome

Of the 6 patients, 3 patients had no improvement in their neurologic status despite treatment. Two patients had improvement in their neurologic status. One patient who initially presented with Brown–Sequard syndrome progressed to quadriplegia. Half of the patients (3 of 6) died of pneumonia secondary to their neurological debilitation, 2 patients in the acute setting and 1 patient several months after the diagnosis of this syndrome. These 3 patients all had quadriplegia at the time of death. One patient died of widely metastatic disease. The remaining 2 patients continue to be seen in our clinic.

### DISCUSSION

Although there are case reports, this is the first series in the literature of patients with a history of SCC of the larynx or hypopharynx describing this syndrome presenting with subtle neck pain progressing to neurological sequela. ORN of the cervical spine was first reported by Lim et al<sup>3</sup> in 1999 and is a rare complication of RT. There have been several case reports in the literature with patients developing ORN of the cervical spine after RT for head and neck malignancies, although most of these cases occurred in patients treated for nasopharyngeal carcinoma.<sup>4–6</sup>

The pathogenesis of this neurological late effect is poorly understood, although several mechanisms have been proposed.<sup>7</sup> RT induces an endarteritis that results in tissue hypoxia, hypocellularity, and hypovascularity with resultant ischemic necrosis of the local tissues including bone.<sup>8–11</sup> In addition, salvage surgery after RT likely causes additional devascularization of the local tissues despite the use of free tissue transplantation in these patients. Fortunately, with the advent of intensity-modulated radiotherapy, there is reduced radiation to the surrounding normal tissues, including the vertebrae.

For the development of the observed neurological late effects, bacterial translocation was a critical event leading to contamination and infection of the epidural space. The exact mechanism of bacterial spread is unknown; however, we speculate that bacteria are seeded via venous hematogenous spread from the pharynx to the venous plexus around the cervical spine. This speculation is supported by the radiologic finding of cord infarction in several patients that was presumably secondary to infectious thrombophlebitis. In addition, in 4 of the patients there was no mucosal disruption and no clear communication with the vertebrae, and particularly the epidural space.

It is concerning that the presenting symptoms are subtle and nonspecific, and once neurological findings are present the progression is rapid and potentially lethal. All of the patients in this study described nonspecific posterior neck and upper back pain localizing to the vertebrae. Many patients also described a posterior headache. Neck pain is a common complaint in patients with head and neck cancer, however, this pain is typically located in the anterior or lateral neck and is most often characterized as burning, tender, sore, or throbbing.<sup>12</sup> In our patients, however, the pain was localized to the posterior neck and back. Although these are fairly nonspecific symptoms, physicians need a high level of suspicion in at-risk

patients with new pain in the spine after any instrumentation of the pharynx. This should prompt a thorough neurologic history and examination to evaluate for subtle signs of early myelopathy, such as weakness, numbness, hyperreflexia, paresthesias, and bowel/bladder incontinence, as this may herald pending neurologic embarrassment. Elevation in the ESR and CRP was a sensitive finding in our cohort. Signs of a systemic inflammatory response may also be present.

Cross-sectional imaging should be obtained in any patient who has posterior neck pain with a history of CRT and salvage laryngectomy who has undergone instrumentation of the pharynx within the last 8 weeks. A CT scan can be used as a helpful screening tool to identify loss of fat in the marrow space of the cervical vertebrae. If loss of fat is present in the cervical vertebrae, an MRI should be emergently performed and neurosurgery should be consulted for possible emergent decompression to avoid severe neurological sequela. Raza et al<sup>13</sup> presented a case report in which a patient previously treated with CRT for SCC of the larynx was seen with neck pain and a headache prompting cross-sectional imaging. The patient did not have any symptoms of myelopathy. The patient underwent occipitocervical fusion and long-term neurologic sequela were avoided, highlighting the need for prompt recognition and early intervention. Similarly, a case was reported by Powell et al<sup>14</sup> in which a patient with radiologic evidence of vertebral ORN was stabilized using a free fibular reconstruction before the development of neurologic symptoms, with no resultant long-term myelopathy.

Antibiotics targeted at pharyngeal organisms should be initiated empirically and expeditiously. A multidisciplinary approach, including infectious disease, neurosurgery, and head and neck surgery, is critical to ensure the best possible outcome. Even with aggressive therapy, the prognosis is poor with a 50% disease specific mortality in our cohort. Of the remaining 3 patients, 2 patients (33%) did have some improvement in their overall neurologic status and 1 patient had stable neurologic disability. This is concordant with the previously reported cases of vertebral ORN in patients treated for SCC of the larynx or hypopharynx. In our review of the literature, we found 6 previously reported cases.<sup>13–19</sup> Collating the outcome of these 6 previously reported cases in the literature, 2 were intervened upon before the development of neurologic sequela, 1 patient had persistent, although improved weakness, 1 survived with quadriplegia, and 2 patients died with quadriplegia secondary to pneumonia.

This syndrome is important to understand. The patients who present with this syndrome are usually well known to the oncology service. They have undergone multiple uneventful dilations and have a delayed onset of vague posterior neck pain that has been present for a few days to a few weeks. The last dilation was usually uneventful and there is no difficulty with voicing or swallowing. These vague symptoms in a trusting doctor-patient relationship can be observed but not acted upon. Unfortunately, once the neurological signs present the timeline becomes very rapid. The neurologic signs are difficult to resolve and the outcome for the patient is not desirable. Because this is not a well-recognized late effect of the treatment of laryngeal or hypopharyngeal cancer it can be

difficult to: first, identify, and second to motivate the multidisciplinary team to act quickly and aggressively. Neurosurgery needs to be encouraged to approach posteriorly through nonradiated tissue and not to wait to see if antibiotics will reverse the neurological signs.

Perhaps a nomenclature would be beneficial for late effects involving specific tissues and sites. The involved structure would be named first, the disease second (ORN), the level of causality, and the primary site of the cancer. For example: vertebral osteoradionecrosis-associated laryngeal cancer. This nomenclature has the breadth to be used across involved structure, disease process, causality, and primary cancer site.

## CONCLUSION

Initial symptoms are usually nonspecific and include posterior neck and back pain as well as headache that develops an average of 27.5 days after either dilation or salvage laryngectomy (range, 9–56 days) with the radiological diagnosis of cervical dural thickening and loss of fat signal in the marrow of the cervical vertebrae being made on average 21.5 days after the onset of pain (range, 1–65 days). The time to diagnosis can be significantly shortened by an increased level of suspicion. Elevation in the ESR and CRP was a sensitive finding in our cohort. Many patients presented with signs of a systemic inflammatory response, such as fever, tachycardia, or hypotension. In the event of epidural fullness, patients are treated with emergent surgical decompression to minimize the progression of neurologic deficits and to offer the best chance of recovery. All patients should be cultured and started on broad-spectrum antibiotics. The i.v. antibiotic course was continued for a minimum of 8 weeks. In our series, a multidisciplinary approach was used with head and neck surgery, neurosurgery, and infectious disease doctors all playing a pivotal role. The prognosis for these patients is grim with the majority of patients failing to recover. The disease-specific mortality in our series was 50% with the patients with the most severe neurologic deficits dying of pneumonia. In the future, early recognition of the importance of subtle posterior neck and upper back pain should decrease mortality and morbidity.

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