Objective: To introduce the concept of neck muscle pain and spasm after radiotherapy and its treatment with botulinum toxin A.

Design: Case series.

Setting: Ambulatory patients at a tertiary care medical center.

Patients: Individuals who had undergone primary or adjuvant radiotherapy for treatment of carcinoma of the head and neck were asked about painful spasms of the neck musculature. A volunteer sample was used. If they desired treatment with botulinum toxin A, they were included in the study.

Intervention: Patients received botulinum toxin A injections to the affected sternocleidomastoid muscle(s) in 1 or 2 locations.

Outcome Measures: Subjective pain relief.

Results: Four of 6 patients with painful tightness of the neck who received botulinum toxin A injections to the sternocleidomastoid muscle achieved pain relief.

Conclusions: A subset of patients with irradiation-induced cervical muscle spasm benefit from treatment with botulinum toxin A injections. Further study is needed to more clearly define the entity and treatment.


Complications from head and neck radiotherapy range from mild xerostomia, dysphagia, muscle atrophy, and soft tissue fibrosis to osteoradionecrosis, hypothyroidism, and spinal cord inflammation or necrosis. Painful chronic bladder spasms have been reported as a consequence of radiation for cervical carcinoma, and trismus has been reported as both an acute and late complication of upper aerodigestive tract radiotherapy with and without concurrent chemotherapy. Radiation-induced trismus due to secondary myokymia of the masseter muscle after treatment for palatal adenocarcinoma has been treated effectively with botulinum toxin A in the past. However, there are no reports in the literature describing painful spasms of the neck musculature after neck radiotherapy. The purpose of this study is to introduce the concept of painful postirradiation muscle spasms of the head and neck musculature specifically of the sternocleidomastoid muscle and the use of botulinum toxin A to help manage the disorder.

RESULTS

Painful spasms of the sternocleidomastoid muscle were identified in 9 patients (3 women and 6 men) with an average age of 65 years (Table). Patients’ complaints ranged from nondescript requests for pain medication for “neck muscle pain” to more specific descriptions of spasms occurring in the sternocleidomastoid muscle lasting seconds to minutes. Eight of the 9 patients received either primary or adjuvant radiation therapy for squamous cell carcinoma of the glottis (2), supraglottis (2), tongue (1), tonsil (1), base of tongue (1), and unknown primary (1). One patient received adjuvant therapy for Merkel cell carcinoma of the cheek, and 1 patient received intra-arterial cisplatin therapy along with radiotherapy on a Radiation Therapy Oncology Group protocol. These 8 patients received an average of 6500 rad (65 Gy) (range, 5400-7400 rad [54-74 Gy]) of radiation to the neck in an average of 37 fractions. The diagnosis of spasms after irradiation was made an average of 37 months (range, 10-62 months)
PARTICIPANTS AND METHODS

Subjects were identified through the University of Iowa Department of Otolaryngology–Head and Neck Surgery, Iowa City. Patients with prior radiotherapy to the head and neck for carcinoma were asked about painful tightness of the neck musculature. A pain rating scale was not utilized. If the patient reported bothersome intermittent tightness and pain, he or she was offered botulinum toxin A injection. Patients with head turning, other involuntary movements associated with the painful tightness, or new-onset cranial nerve deficit were excluded from this study as were those with evidence of recurrent disease or trauma or surgery to the head or neck within the past month.

Written informed consent was obtained prior to treatment. Before the toxin injection, local anesthetic (approximately 1 mL of 1% lidocaine with epinephrine, 1:100 000) was infiltrated subcutaneously using a 30-gauge needle over the sites of planned injection (Figure). Toxin injections were performed into the substance of the sternocleidomastoid muscle in 2 sites using a 27-gauge Teflon needle connected to a system specifically designed to audibly monitor electromyographic (EMG) activity during the botulinum toxin A injection. The EMG system was used to confirm placement of the needle in the sternocleidomastoid muscle and not to identify abnormal patterns of EMG activity. Palpation of the carotid pulse was done to direct the injection away from this structure. The patient’s age, sex, original tumor site, histologic type, TNM classification, total delivered radiation dose, number of fractions delivered, number of months from the end of radiation treatment to diagnosis, initial dose of botulinum toxin A injected, number of sequential injections and doses, as well as time between injections and subjective change in pain were all determined from the patient’s chart.

Six patients (2 women and 4 men) have been injected with botulinum toxin A. One patient’s pain was unchanged pain after injection of 25 U and was therefore labeled as a nonresponder. This patient had very little audible EMG activity noted when the toxin was injected. A second patient had an inadequate response after 2 injections (25 U each injection, 3 months apart) and subsequently deferred further injections. The remaining 4 patients have had complete relief of symptoms after completion of radiotherapy. Two patients had prior selective neck dissections (levels II–IV) on the affected side. The patient with an unknown primary tumor had a modified radical neck dissection sparing cranial nerve XI on the affected side, and cranial nerve XI function was clinically normal. This patient did not receive a toxin injection. The 1 patient with a base of tongue tumor had a modified radical neck dissection sparing cranial nerve XI and no surgical procedure on the affected side. The patient with an unknown primary tumor had selective neck dissections (levels II–IV) on the affected side. The patient with an unknown primary tumor had selective neck dissections (levels II–IV) on the affected side. The patient with an unknown primary tumor had selective neck dissections (levels II–IV) on the affected side.

In early studies of radiation biology, muscle and peripheral nerves were thought to be relatively radioresistant. It is now clear that radiation treatment has both acute and late effects on muscles and peripheral nerves, although late effects predominate and are dose dependent. With one-time doses up to 3000 rad (30 Gy) and fractionated doses up to 8000 rad (80 Gy) (when the dose per fraction was <270 rad [<2.7 Gy]), animal studies have shown few effects on muscle histologic features for the first 3 to 4 weeks after therapy. However, as early as 2 to 4 months after a one-time 2000 rad (20 Gy) treatment, focal areas of loss of capillaries with muscle degeneration develop. Increase in collagen and decrease in proteoglycans in the extracellular matrix follows and leads to disorganized structure and tissue fibrosis. The effect can be progressive for up to 2 to 5 years and appears to be related to the dose of radiation therapy. Based on data from patients after radiation for carcinoma of the tonsil, Withers et al demonstrated that the incidence of severe muscle and bone complications designated as grade III and IV by the modified Radiation Therapy Oncology Group/European Organization Research on the Treatment of Cancer late radiation morbidity scoring scheme continue to rise indefinitely as time from radiotherapy increases. Grade III complications consist of severe in- duration or loss of tissue, severe trismus, severe pain, self-limited necrosis, or bone exposure. Grade IV complications consist of necrosis requiring surgery or leading to spontaneous fracture. Mucosal complications, however, plateau after approximately 1 year. Karasek et al
induced cranial nerve injury is rare.10 The addition of chemotherapy to radiation treatment. This interval from treatment to development of spasms is consistent with the time course for late muscular complications to develop. The patient group received between 5400 and 7400 rad (54-74 Gy) in an average of 37 fractions, and thus are above the dosage expected to increase the risk of complication. The ongoing muscle damage, remodeling, and fibrosis in these patients may contribute to muscle excitability and lack of soft tissue elasticity leading to painful spasms.

Irradiation has both acute and late effects on the peripheral nerve. The acute, direct effects have been shown to be associated with EMG and chemical changes. Long-term human and animal studies have shown radiation treatment induces a decrease in Schwann cell proliferation leading to demyelination and long-term fibrosis of the nerve fibers and the nerve sheath. This effect has been shown to occur in dogs with single doses greater than 2000 rad (20 Gy). Demyelination is known to cause pain associated with spasm, especially in progressive demyelinating diseases such as multiple sclerosis of which trigeminal neuralgia and bladder spasms are common manifestations. Postirradiation muscle spasm differs from a dystonia in that there is no abnormal involuntary movement of a twisting and sustained nature as there is in torticollis. However, it more closely clinically resembles myokymia, which is a disorder characterized by muscular twitching. The diagnosis of myokymia requires EMG evidence of continuous, irregular motor-unit discharges. Brachial and lumbosacral radiation have been reported to induce secondary myokymia.8,9 While this clinical entity may represent a form of cervical myokymia, the EMG data to confirm this diagnosis were not obtained as part of this study. However, severe head and neck radiation-induced cranial nerve injury is rare.10

The addition of chemotherapy to radiation protocols does not appear to change the late muscle effects of radiation.10 Only 1 patient in this group received intraarterial cisplatin, so the effect of adding chemotherapy to radiotherapy on neck muscle spasms could not be evaluated.

<table>
<thead>
<tr>
<th>Patient No./Sex/ Age, y</th>
<th>Tumor Site</th>
<th>TNM Classification</th>
<th>Histologic Type</th>
<th>Total Radiation Dose, rad (Gy)</th>
<th>Total Fraction</th>
<th>Posttherapy, mo</th>
<th>Initial Toxin Dose, U</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/64</td>
<td>Left cheek</td>
<td>NA</td>
<td>Merkel cell</td>
<td>6000 (60)</td>
<td>60</td>
<td>39</td>
<td>20</td>
</tr>
<tr>
<td>2/M/60</td>
<td>Glottis</td>
<td>Tis N0</td>
<td>Microinvasive</td>
<td>6600 (66)</td>
<td>33</td>
<td>11</td>
<td>25</td>
</tr>
<tr>
<td>3/N/45</td>
<td>Tongue</td>
<td>T1 N1</td>
<td>SCC</td>
<td>5400 (54)</td>
<td>27</td>
<td>51</td>
<td>25</td>
</tr>
<tr>
<td>4/M/64</td>
<td>Supraglottis</td>
<td>T2 N1</td>
<td>SCC</td>
<td>7400 (74)</td>
<td>46</td>
<td>48</td>
<td>25</td>
</tr>
<tr>
<td>5/F/75</td>
<td>Supraglottis</td>
<td>T2 N0</td>
<td>SCC</td>
<td>7000 (70)</td>
<td>35</td>
<td>42</td>
<td>15</td>
</tr>
<tr>
<td>6/M/72</td>
<td>Left TVF</td>
<td>T2 N0</td>
<td>SCC</td>
<td>6000 (60)</td>
<td>30</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>7/N/55</td>
<td>Left neck</td>
<td>TX N2</td>
<td>SCC</td>
<td>6600 (66)</td>
<td>31</td>
<td>24</td>
<td>NA</td>
</tr>
<tr>
<td>8/M/76</td>
<td>Left tonsil</td>
<td>T2 N0</td>
<td>SCC</td>
<td>7000 (70)</td>
<td>35</td>
<td>62</td>
<td>NA</td>
</tr>
<tr>
<td>9/F/78</td>
<td>BOT</td>
<td>T2 N2</td>
<td>SCC</td>
<td>7000 (70)</td>
<td>35</td>
<td>50</td>
<td>NA</td>
</tr>
<tr>
<td>Mean age, 65</td>
<td></td>
<td></td>
<td></td>
<td>6556 (65.56)</td>
<td>37</td>
<td>37</td>
<td>22</td>
</tr>
</tbody>
</table>

*SCC indicates squamous cell carcinoma; TVF, true vocal fold; NA, not applicable; BOT, base of tongue.

Relatively small doses of botulinum toxin A have been effective in treating symptoms in this patient group. Initial doses averaged 22 U to each affected muscle. This range is significantly smaller than the doses required to control torticollis (75-100 U). Therefore, the injection is less likely to diffuse to adjacent sites to impair swallowing function and other side effects of sternocleidomastoid toxin injection. In addition, using smaller doses lessens the likelihood of developing resistance to therapy.

In treatment of cervical dystonia, it is well established that botulinum toxin A therapy is superior to placebo.11 Recently, Hilker et al12 have shown that not only is there a measurable clinical response to antispasmodic therapy, but patients’ scores on validated health-related quality-of-life instruments (EuroQol [EQ-5D] and the Short-Form 36-Item Health Survey questionnaire [SF-36]) improve. In general, patients with focal dystonia scored lower on initial testing than the general population as it relates to health-related quality of life. Botulinum toxin A therapy significantly improved the SF-36 and EQ-5D quality-of-life scores in all but the SF-36 physical functioning, role-emotional, and general health dimensions at the first follow-up visit (6 weeks after injection). All dimensions returned almost to baseline at the second follow-up visit (12 weeks after injection) as might be expected based on the mechanism of action of botulinum toxin A. Further study is needed to determine the effect of botulinum toxin A therapy for patients with postirradiation muscle spasm on patient’s quality of life.

This study is limited by its small sample size. Further studies are required to electromyographically characterize the muscle activity, to compare the analgesic effect of the local anesthetic injection without the subsequent toxin injection, and to determine the time of onset of the symptoms. Additionally, other muscles within the radiation field (eg, trapezius, splenius, and levator) were not targeted in this study; however, they have the potential to contribute to painful neck spasms.

**CONCLUSIONS**

In this preliminary study, we have described neck muscles spasms after radiotherapy in a small number of...
Two thirds (4 of 6) of patients benefited from treatment of the affected sternocleidomastoid muscle with botulinum toxin A therapy. More research is needed to clarify the etiology, incidence, predisposing factors, time course of spasm development, and association with combined chemotherapy and radiation dose dependency.

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REFERENCES


