A 5-year-old castrated male Maltese was examined by the referring veterinarian because of a 4-month history of progressive and intermittent clinical signs of muscle cramping and abnormal movements of the skin of the right pelvic limb at the site where an infiltrative lipoma had twice been resected. Two years prior to examination, a lipoma that was approximately 4 cm in diameter was initially resected from the muscles at the caudal aspect of the right thigh. One year later, a palpable mass was identified at the same location. It was suspected that the lipoma had recurred, and a second resection was performed without preoperative diagnostic imaging to determine the extent of the tumor. Radiation therapy of the surgical field was recommended following the second resection, and the dog’s owner decided to pursue RT 3 weeks after the second surgery. At that time, CT was performed on the right pelvic limb to assess the surgical site and develop a plan for RT. Evaluation of the CT images did not reveal any residual tumor tissue. Radiation therapy was performed with a linear accelerator. The RT protocol was developed by manual treatment planning on the basis of measurements obtained from the linear accelerator’s output, a cone factor of 1, and a prescribed dose to the 90% isodose line. The protocol was designed by a board-certified radiation oncologist, but it was not evaluated by a physicist. The prescribed radiation dose was nineteen 3-Gy fractions (total radiation dose, 57 Gy) to be administered to the surgical field on a daily basis for 5 days (Monday through Friday) and was consistent with a definitive intent treatment.

For each treatment, anesthesia was induced with propofol (5 mg/kg [2.3 mg/lb], IV) and maintained with isoflurane. The dog was positioned in lateral recumbency with the right pelvic limb placed and

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**Abbreviations**

BED Biological effective dose  
BoNT-A Botulinum toxin type A  
EMG Electromyography  
RT Radiation therapy  

**Case Description**

A 5-year-old castrated male Maltese was evaluated for intermittent clinical signs of muscle cramping and abnormal movements of the skin of the right pelvic limb at the site where an infiltrative lipoma had twice been resected. After the second surgery, the surgical field was treated with radiation therapy (RT). The clinical signs developed approximately 14 months after completion of RT.

**Clinical Findings**

When clinical signs were present, the right biceps femoris and semitendinosus muscles in the area that received RT were firm and had frequently visible contractions, and the skin overlying those muscles had episodic vermiform movements. Electromyography of those muscles revealed abnormal spontaneous activity with characteristics consistent with myokymic discharges and neuromyotonia. Magnetic resonance imaging of the affected leg revealed no evidence of tumor regrowth. The myokymia and neuromyotonia were considered secondary to RT.

**Treatment and Outcome**

4 U of *Clostridium botulinum* toxin type A (BoNT-A) neurotoxin complex was injected into the affected muscles at each of 6 sites twice during a 24-hour period (ie, 48 U of BoNT-A were administered). The clinical signs were completely resolved 10 days after BoNT-A treatment and were controlled by repeated BoNT-A treatment every 3 to 4 months for >1 year.

**Clinical Relevance**

To our knowledge, this is the first report of myokymia and neuromyotonia secondary to RT in a dog. For the dog of this report, injection of BoNT-A into the affected muscles was safe, effective, and easy to perform. (J Am Vet Med Assoc 2016;248:532–537)
secured on a foam positioning device; 0.5-cm-thick bolus material was used during RT. Because the estimated tissue depth of the resected tumor was 2.5 to 3.0 cm, the radiation was delivered as a single 10-MeV electron beam. The beam was directed laterally relative to the limb. The planned target volume of tissue irradiated was determined by measuring 4 cm in all directions from the approximately 5-cm-long surgical scar and delineating that perimeter by marking the skin with an ink pen. A 10 × 10-cm electron beam cone was used. The field size was reduced further by the use of lead strips to a final size of 8 × 10 cm. Quality assessment of the linear accelerator was performed daily; but in vivo dosimetry was not performed. Radiographic images to ensure consistent patient positioning (eg, port films) during RT were also not obtained. Instead, the surgical scar and ink marks on the skin were used to ensure consistent patient positioning for RT. Radiation therapy was administered without any delays, interruptions, or deviations from the prescribed plan. No medications or additional treatments (other than the anesthetic agents) were administered during or within 16 days after RT.

Sixteen days after completion of RT, the dog developed skin lesions and signs of pain at the radiation site, and hydrotherapy and administration of tramadol⁶ (3.6 mg/kg [1.6 mg/lb], q 6 h for 10 days) and carprofen² (1.8 mg/kg [0.82 mg/lb], q 12 h for 10 days) were initiated. During and following RT, it was recommended that the dog wear an Elizabethan collar as much as possible to prevent it from licking and chewing at the treatment area; however, the owner admitted to being noncompliant with this recommendation. Consequently, it was believed that the skin lesions were the result of the dog licking and chewing at the irradiated site, although an adverse skin reaction to the RT could not be ruled out. On the basis of appearance, the lesions were considered a grade 2 adverse skin effect on the Veterinary Radiation Therapy Oncology Group grading scale.¹ The skin lesions and signs of pain resolved within 1 week after hydrotherapy and analgesia were initiated.

Fourteen months after completion of RT, the dog developed intermittent episodes of what the owner perceived were signs of muscle cramping and abnormal movements of the skin and muscles in the area of the radiation field on the right pelvic limb. Those episodes lasted for approximately 1 minute and occurred several times daily. Initially, the dog was treated with biweekly laser⁴ and physical therapy on the right pelvic limb, then a holistic approach that included acupuncture and administration of herbal supplements (types and amounts unknown) was tried for 4 months. The clinical signs became more severe and frequent despite treatment, and the dog was referred to a tertiary hospital.

During the initial physical and neurologic examinations performed at the tertiary hospital, the only abnormalities observed were right pelvic limb lameness and an area of alopecia over the right caudalateral aspect of the thigh at the RT site. Because the clinical signs were intermittent, the owner provided a video of an episode that showed the dog intermittently carrying (ie, not bearing weight on) the right pelvic limb in extension and slightly abducted while walking or running. The dog eventually sat down as the episode continued. After several examinations at the primary care and tertiary hospitals over a period of 5 months, the dog finally had an episode during an examination. That episode appeared to be involuntary and had an acute onset and short duration, lasting approximately 1 minute. During the episode, the right biceps femoris and semitendinosus muscles within the radiation field at the caudal aspect of the right thigh were contracted and firm on palpation. The dog cried out and tried to bite when those muscles were palpated, which suggested that they were painful. Following the episode, no abnormalities were palpated in the affected muscles and the dog did not have any further signs of pain. Those findings were most consistent with neuromyotonia, a syndrome characterized by persistent muscle contraction and stiffness with impaired relaxation.²

The dog also had intermittent vermiform movements of the skin overlaying the affected muscles at the RT site. Those movements were not always associated with the signs of muscle cramping and, in fact, were more frequent than the episodes of involuntary muscle contraction, which occurred every few minutes during the examination and lasted for 30 to 60 seconds. The observed vermiform movements of the skin resembled the clinical description for focal myokymia, a localized area of involuntary continuous muscle fiber activity.²

Results of a CBC and serum biochemical analysis, including creatine kinase activity, were all within reference limits. No abnormalities were detected on thoracic radiographs. The lumbosacral vertebral column was assessed by use of a 1.5-T MRI unit,⁴ and no abnormalities were detected in the lumbar and sacral portions of the spinal cord, its dorsal and ventral roots, and associated nerves. The right pelvic limb was also assessed by MRI, and the following sequences were obtained: T1-weighted and T2-weighted images in the sagittal and transverse planes and T1-weighted images with chemical fat saturation following administration of gadopentetate dimeglumine² (0.2 mL/kg [0.09 mL/lb], IV). Results revealed no evidence of tumor recurrence in the muscles of the right thigh, and the subjective intensity of the muscles was considered normal, although it is difficult to differentiate clinically normal fat from an infiltrative lipoma.

The dog was anesthetized, and standard needle EMG⁸ of the muscles of the pelvic limbs was performed. The EMG results indicated that the right biceps femoris and semitendinosus muscles had abnormal spontaneous electrical activity that consisted of doublet and multiplet discharges of single motor units (Figure 1). The amplitudes varied between 200 and 450 μV and occurred with an interburst frequency that ranged between 60 and 70 Hz and an intraburst frequency that

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ranged between 280 and 570 Hz. The trains of waveforms started and stopped spontaneously. Those findings were characteristic of both neuromyotonic and myokymic discharges. The abnormal discharges were present only in the muscles at the caudal aspect of the right thigh that had grossly visible myokymia and were absent in the other muscles of the right thigh and the muscles at the caudal aspect of the left thigh.

The clinical signs continued to worsen despite empirical treatment, and alternative treatment options were pursued. Nineteen months after completion of RT and 5 months after manifestation of clinical signs, 4 U of BoNT-A was injected IM at each of 6 sites that were equally spaced within the 10 X 10-cm previous radiation field at the caudal aspect of the right thigh. The dose of BoNT-A injected was estimated on the basis of information provided in a previous case report in which BoNT-A was administered to a dog with generalized myoclonus. The injections were performed twice, approximately 6 to 8 hours apart; thus, a total of 48 U of BoNT-A was injected into the affected area. After each treatment, the injected muscles were massaged and the limb was moved through various ranges of motion to facilitate distribution of the BoNT-A through the tissue. No external coaptation or movement restrictions were implemented during or after the BoNT-A injections.

For 4 days after the BoNT-A treatment, the dog was monitored for adverse reactions and underwent daily physical and neurologic examinations, with special attention paid to gait analysis and assessment for signs of weakness. No adverse reactions to the BoNT-A were observed. The dog was then evaluated weekly for 2 months. The dog's owner reported that the intermittent myokymia and signs of muscle cramping and neuromyotonia ceased within 10 days after the BoNT-A injections. No clinical signs were observed during any of the subsequent physical and neurologic examinations in the 2-month monitoring period. Three months after the BoNT-A treatment, the owner reported that the clinical signs had returned. Subsequently, the BoNT-A injection protocol was repeated every 3 to 4 months as necessary to resolve or prevent recurrence of clinical signs. At the time this report was written (19 months after onset of clinical signs), the dog had been treated with BoNT-A 7 times and was still alive without recurrence of clinical signs or the infiltrative lipoma.

Discussion

The present report provided anecdotal data about the treatment, efficacy, and safety of BoNT-A injections into specific muscles of a dog for the reduction of myokymia and neuromyotonia induced by RT. Myokymia and neuromyotonia are believed to be 2 clinical manifestations on a continuum of motor nerve terminal hyperexcitability that can be distinguished by EMG. Myokymia is defined as involuntary undulating vermiliform movements of the skin caused by contraction of small bands of muscle fibers that can be focal or generalized. During EMG examination, myokymia is characterized by short bursts (< 0.5 seconds) of single motor unit potentials spontaneously firing at a frequency of 5 to 150 Hz at regular or irregular intervals after a period of silence. Neuromyotonia is characterized by involuntary sustained contractions of the affected muscles; neuromyotonic discharges fire in bursts at frequencies of 150 to 300 Hz for 0.5 to 2.0 seconds (ie, neuromyotonic discharges are more prolonged than myokymic discharges) with waning amplitude and often start and stop suddenly. Myokymia and neuromyotonia are thought to be aspects of the same underlying abnormality.

In veterinary medicine, both generalized and focal forms of myokymia and neuromyotonia have been described. Most of the case reports that describe
generalized myokymia and neuromyotonia involve Jack Russell Terriers. In Jack Russell Terriers with myokymia and neuromyotonia, pathophysiologic changes are thought to be associated with alterations (either from destruction of potassium channels by the immune system or overactive sodium channels) in the voltage-gated ion channels of muscles that result in persistent depolarization. Affected dogs have been treated with sodium-channel blockers with varying results. Generalized myokymia leading to collapse has been reported in a crossbred dog, Border Collie, 2 Yorkshire Terriers, and 3 Jack Russell Terriers. Generalized neuromyotonia and myokymia of unknown origin have also been described in a cat. In previous reports of dogs with focal myokymia and neuromyotonia, only facial muscles have been affected, and the underlying causes were intracranial meningioma, pituitary adenoma, and inflammatory CNS disease. The dog of the present report had vermiciform movements of the skin and intermittent sustained contractions of the underlying muscles in a focal area of the right pelvic limb, clinical signs that were most consistent with focal myokymia and neuromyotonia. During EMG, burst frequencies were most consistent with neuromyotonia, but the burst durations were < 0.5 seconds, which was most consistent with myokymia. Because the MRI images of the right pelvic limb obtained 5 months after clinical signs of myokymia began to manifest revealed no abnormalities, it is unlikely that the myokymia and neuromyotonia were the result of recurrence of the infiltrative lipoma, although microscopic regrowth of the tumor cannot be excluded.

Focal myokymia isolated to an arm or leg has been associated with RT-induced brachial plexopathy and sciatic neuropathy in human cancer patients. Post-radiation neuropathies affecting the femoral nerve, cranial nerves, and lumbosacral plexus have also been described in human patients. Radiation therapy-induced myokymia may develop as a delayed adverse effect of RT, resulting in the demyelination of an irradiated nerve, which leads to membrane instability as well as ischemic injury and fibrosis secondary to vascular endothelium damage.

For the dog of this report, diagnosis of RT-induced myokymia was supported by the dog’s history of receiving RT in conjunction with gross evidence of myokymia within the radiation field, EMG results, and the lack of MRI evidence of lipoma recurrence in the affected area. In dogs, the rationale for diagnosis of RT-induced myokymia is similar to that for human patients, and MRI is used to distinguish between RT-induced myokymia and early tumor infiltration. Neoplasia is rarely a direct cause of myokymia in human patients; however, an intracranial meningioma was identified as the direct cause of facial myokymia in 1 dog. Local infiltration of a neoplasm into a muscle generally does not cause myokymic discharges on EMG recordings; therefore, EMG abnormalities are more frequently associated with RT-induced myokymia than neoplasia. Individuals with myokymia secondary to neoplastic infiltration can have clinical signs similar to those of individuals with RT-induced myokymia. Although rare, RT-induced neuropathy and RT-induced myokymia in particular typically develop in human patients > 1 year after completion of RT. For patients that develop RT-induced brachial plexus neuropathy, the median interval between completion of RT and the development of clinical signs is 1 to 4 years. For the rare patients that develop myokymia secondary to neoplastic infiltration, clinical signs generally manifest within 1 year after diagnosis of the neoplasia, although there is substantial variation among patients. The dog of the present report developed clinical signs 14 months after completion of RT, which is most consistent with RT-induced myokymia.

The development of RT-induced injury to the peripheral nervous system is multifactorial. In human patients, the risk for RT-induced brachial plexus neuropathy, including myokymia, increases from 1.7% to 73% as the total radiation dose increases from 43.5 to 60 Gy. The likelihood of RT-induced brachial plexus neuropathy also increases as the radiation dose per fraction increases. Although those findings support a positive association between total radiation dose and RT-induced injury, direct comparisons between those findings and the total radiation dose received by the dog of this report should be done with caution because the total radiation dose in and of itself does not adequately account for the complex effects of RT on the peripheral nervous system. Nerves are fairly radioresistant and have a low α/β ratio (measure of the radiation dose-response curve) that ranges between 2 and 3.5 Gy. Few studies have been conducted to comprehensively investigate dogs with RT-induced neuropathies. In an experimental setting, clinical, electrophysiologic, and histologic evidence of RT-induced neuropathy was not detected in dogs that received twenty-five 2-Gy fractions (total radiation dose, 50 Gy), thirty 2-Gy fractions (total radiation dose, 60 Gy), thirty 2.53-Gy fractions (total radiation dose, 70 Gy), or thirty 2.67-Gy fractions (total radiation dose, 80 Gy) of RT over a 5 × 10-cm field by use of bilaterally opposed fields. Radiation therapy fractionation schedules are most accurately compared on the basis of the BED. The BED is a measure of the radiation dose delivered to a specific tissue that takes into account the α/β ratio of that tissue and thereby reflects the tissue’s inherent radiobiological properties. It is calculated by use of the following equation: BED = nd X (1 + d/α/β ratio), where n is number of fractions and d is the radiation dose per fraction. When a commonly used value of 3 was used for the α/β ratio, the BED for the fractionation schedule used for the dog of the present report was 114 Gy, (nineteen 3-Gy fractions). The BEDs for the 4 fractionation schedules used in the experimental study were 83 (twenty-five 2-Gy fractions), 90 (thirty 2-Gy fractions), 124 (thirty 2.33-Gy fractions), and 152 (thirty 2.67-Gy fractions) Gy, respectively. The dog of the present study developed a
neuropathy, even though the BED for the fractionation schedule used in that dog fell within the range of BEDs for the fractionation schedules that failed to produce neuropathies in the dogs of the experimental study. Other factors such as differences in the volume of tissue treated (greatest for the dog of the present report), inherent dosing variability among electron beams, and potential patient-specific variables (eg, postoperative scarring and fibrosis) likely contributed to the development of myokymia in the dog of this report.

On histologic evaluation, RT-induced neuropathy appears to involve fibrosis of the epineurium, which likely results in entrapment of the affected nerves and secondary demyelination and vascular compromise. For the dog of the present report, the history, clinical signs, and EMG and MRI findings were sufficient to support a diagnosis of RT-induced myokymia. Biopsy specimens of the affected muscles and nerves were not obtained because it was suspected that histologic changes consistent with RT-induced neuropathy would contribute little to the development of a treatment strategy for the dog.

In human patients with myokymia, initial treatment typically includes skeletal muscle relaxants and cellular membrane stabilizers such as carbamazepine or phenytoin. Botulinum toxin type A injections are generally recommended only for patients that fail to respond to initial treatment. Botulinum toxin type A is a neurotoxin produced by Clostridium botulinum, a sporulating, rod-shaped, gram-positive anaerobe that acts at the neuromuscular junction within the nerve terminal by cleaving synaptosomal-associated protein 25 in the acetylcholine vesicle membrane, which prevents the presynaptic vesicle from fusing with the presynaptic membrane and effectively blocks acetylcholine release and neuromuscular transmission. When BoNT-A is injected IM, muscle relaxation occurs in a dose-dependent manner. Blockage of acetylcholine transmission at the neuromuscular junction induced by BoNT-A is transient because of receptor regeneration, and muscle strength is generally restored within 3 to 4 months. The effects of BoNT-A are typically observed within 1 to 3 days after injection in most human patients but may not be noticeable for 1 to 2 weeks in some patients. The peak effect of BoNT-A generally occurs 2 to 4 weeks after injection, and the effects typically last for 4 to 8 weeks and then gradually dissipate. In human patients, adverse effects associated with BoNT-A include lethargy, pyrexia, pain, weakness, and urinary incontinence.

Botulinum toxin type A is used to treat various clinical conditions in human patients such as trismus associated with RT-induced myokymia and muscle spasms, muscle contracture in children with cerebral palsy, and intractable orbicularis myokymia. The use of BoNT-A in interventional neurology continues to evolve and grow because of the low incidence of adverse effects associated with its administration. In human patients, the treatment benefits and duration of action of BoNT-A increase with successive treatments. Repeated injection of BoNT-A does not appear to elicit production of antibodies against the toxin; therefore, from a hypothetical standpoint, BoNT-A injections can be administered indefinitely.

Compared with humans, dogs have a natural resistance to all types of botulinum toxin; however, although the time to onset of effects after BoNT-A injection is similar, the duration of action is shorter and the clinical effect achieved by an equivalent dose is less. In dogs, BoNT-A has been used experimentally to induce temporary ptosis and clinically to treat essential blepharospasm, ptalism and rhinorrhea, and myoclonus secondary to suspected canine distemper encephalomyelitis. In general, BoNT-A represents a reversible, safe, effective, and minimally invasive alternative to more radical interventions such as limb amputation, neuroectomy, or myectomy.

To our knowledge, the present report is the first to describe RT-induced myokymia and neuromyotonia in a dog. Although this report involved only 1 dog, the clinical signs observed in the dog mirrored those observed in human patients with RT-induced myokymia and neuromyotonia. The dog of this report was successfully treated with BoNT-A. Additional dogs with similar clinical signs need to be identified and treated with BoNT-A to substantiate the efficacy of the toxin for treatment of myokymia and neuromyotonia and elucidate its potential adverse effects.

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Footnotes

a. Primus 6-MV linear accelerator, Siemens Medical Systems, Concord, Calif.
b. Tramadol, Ortho-McNeil, Raritan, NJ.
d. Veterinary laser; Cutting Edge Laser Technologies, Fairport, NY.
e. 1.5-T Signa Excite, GE Healthcare, Waukesha, Wis.
g. Siemens Wedge II, Cadwell Laboratories Inc, Kennewick, Wash.
h. Botox, Allegran, Irvine, Calif.

References


