ORIGINAL ARTICLE

Use of Botulinum Toxin Type A for Chronic Cough

A Neuropathic Model

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Objective: To review the experience and outcomes of a novel use of botulinum toxin type A (BtxA) in the treatment of chronic cough.

Design: Retrospective case series.

Setting: Academic referral center.

Patients: A total of 438 patients were diagnosed as having laryngeal spasm and chronic cough, and 6 were documented as having chronic cough treated with BtxA injections. Two patients were excluded from the study because of a history of tracheostomy or concurrent laryngeal and voice dysfunction.

Intervention: Electromyography-guided BtxA injections of the thyroarytenoid muscles.

Main Outcome Measures: Patient demographics (age and sex), voice-related quality-of-life scores, postprocedure complications, number of BtxA units used, number and length of treatments, and voice outcomes are reviewed.

Results: Three of the 4 patients (75%) were women, and the mean patient age was 55.6 years (range, 38-64 years). All patients had significant relief of cough after BtxA injection, with complete resolution after a median of 7 injections (range, 4-16), using a mean dose of 4.0 U (range, 1.0-10.0 U) per treatment session for a mean duration of 25.7 months (range, 7.2-42.9 months).

Conclusions: To our knowledge, this is the first reported series in the literature of the use of BtxA in the treatment of chronic cough in adults. In this small case series, we report a neuropathic model for chronic cough caused by neuroplastic changes and laryngeal hyperactivity as an explanation for the effectiveness of BtxA treatment. Further research and long-term follow-up are warranted, but BtxA is effective in directly decreasing laryngeal hypertonicity and possibly reducing neurogenic inflammation and neuropeptide-mediated cough. Botulinum toxin type A can be considered for the treatment of chronic cough refractory to other medical therapies.

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COUGH IS ONE OF THE CHIEF complaints in the primary care setting. Cough is a symptom, not a diagnosis, and it usually remits after the underlying condition resolves. However, cough can persist in some patients despite extensive medical workup and multiple therapies. The cough reflex is mediated by a variety of afferent and efferent neurologic pathways and has numerous causes.

Cough can be classified by anatomy, with tracheobronchial (eg, asthma, bronchitis, or tracheal stenosis), laryngeal (eg, vocal fold paralysis or neoplasm), or sinonasal (eg, allergies, postnasal drip, or rhinosinusitis) causes.[1] Cough can also be classified by source of stimulus, including chemical, mechanical, or inflammatory mediators.[1]

The neurologic pathway of the cough reflex involves a complex interaction of sensory and motor mechanisms. The cough reflex begins when a stimulus activates a sensory receptor to stimulate an afferent signal to the brainstem through various neuropeptides. This information is integrated in the brainstem, with possible interactions from the cerebral cortex, and results in an efferent signal of motor instructions to coordinate a cough.[1] Coughing requires a sequence of several steps. First, deep inspiration, glottic closure, and relaxation of the diaphragm allow generation of increased airway pressure. Second, the thoracic muscles contract and bronchial smooth muscles constrict as the glottis opens. Third, a marked increase of airway flow produces a cough, with shearing forces for the expulsion of mucus or foreign material.[1]

The cough reflex helps protect the airway by expelling mucus or noxious material. When this normal process is dysfunc-

tional, chronic cough can develop. Chronic cough is defined as cough that persists for more than 3 weeks[2] despite treatment. The most common causes of cough are asthma, allergic rhinosinusitis, laryngopharyngeal reflux, chronic bronchitis, and chronic rhinosinusitis. Proper diagnosis and treatment are effective in treating symptoms of cough. However, there is a small subset of patients for whom cough persists despite treatment. These patients present a diagnostic and therapeutic challenge and are often given a nonspecific diagnosis of chronic cough.

Patients with chronic cough likely represent a heterogeneous group of disorders with multifactorial causes and a common laryngeal response. Chronic cough is often misdiagnosed as irritable laryngeal syndrome (ILS), paradoxical vocal fold motion (PVFM), Munchausen stridor, factitious asthma, hysterical or psychogenic asthma, episodic paroxysmal laryngospasm, functional laryngeal stridor, laryngeal dyskinesia, or involuntary adduction during inspiration.[3] Chronic cough, also known as habit cough or psychogenic cough, is believed to be caused by a dysfunction in neurologic activity. This entity is poorly understood, and there is no consensus for diagnosis or management. Recent literature[4-6] has suggested a neuropathic model for chronic cough, likened to other cranial nerve disorders, such as Bell palsy, trigeminal neuralgia, glossopharyngeal neuralgia, and postviral vagal and olfactory disorders. Vagal neuropathy can affect the larynx through sensory and motor nerves by causing vocal fold paresis or laryngeal pain or irritation. Behavioral therapy has been suggested[6] to address the neurologic and psychogenic component, as well as other anecdotal therapies aimed at neuropathic pain or neurogenic hypersensitivity.[1,7-9]

We report a case series of 4 patients without any identifiable cause of chronic cough who had thorough workups and empirical treatment without success, including aggressive pharmacotherapy for reflux, asthma, allergies, and over-the-counter therapies. All 4 patients were successfully treated with botulinum toxin type A (BtxA) injections, and we hypothesize laryngeal hypertonicity and inappropriate neurologic feedback as the causes of chronic cough in these patients. We discuss the mechanisms of cough and pharmacologic activity of BtxA as a potential treatment of neuropathic chronic cough.

METHODS

The institutional review board approved a review of all patient records from July 1, 2003, through March 31, 2009, at a single, academic, tertiary referral center for diagnoses of laryngeal spasm and chronic cough. A total of 438 patients were identified and, of those, 6 were documented to have chronic cough treated with BtxA injections. One patient was excluded because of a history of multiple tracheostomies and another patient was excluded because she currently had spasmodic dysphonia treated with BtxA injections. The remaining 4 patients had significant disruption of function and quality of life despite exhaustive workup and conservative, empirical treatment of chronic cough. Botulinum toxin type A injections were offered as a possible treatment after informed consent, rationale of therapy, explanation of off-label use, and disclosure of possible adverse effects, such as temporary breathiness and decreased voice quality. The patients, treatment, and outcomes are reviewed.

PATIENT 1

Patient 1 was a 64-year-old attorney who had a 30-month history of chronic cough, which began after an episode of pneumonia and pertussis infection. His cough was consistently triggered with initiation of phonation, which severely limited his ability to work and led to early retirement. He did not report hoarseness or other changes in voice quality. The results of his workup were negative for allergic rhinitis, reflux disease, shortness of breath, or pulmonary origins. He did not use tobacco or alcohol. The patient had previously been evaluated at 3 other tertiary medical facilities and treated with antireflux medications, allergy medications, multiple antibiotics, systemic and inhaled corticosteroids, antitussive medications, mucolytics, cough suppressants, and voice therapy. All previous treatments did not provide any improvement. His chief complaint was the inability to speak without coughing, which had caused him to retire from his work as an attorney and withdraw socially. Findings on physical examination were unremarkable except that the patient had a dry cough only when speaking. His initial voice-related quality-of-life (VRQOL) score was 20, and videostroboscopy revealed normal vocal fold mobility with no mucosal abnormalities.

PATIENT 2

Patient 2 was a 38-year-old teacher who had an 8-month history of chronic cough. She had a history of asthma confirmed by pulmonary function testing, allergic rhinosinusitis, and allergies to trees, pollen, and mites confirmed by skin testing. She also had a small hiatal hernia diagnosed by barium swallow. Her cough was triggered by phonation and worsened at night. Previous treatment with albuterol sulfate, theophylline, mucolytics, cough suppressants, proton pump inhibitors, immunotherapy, allergy medications, and voice therapy provided minimal improvement. Physical examination revealed signs of extraesophageal reflux but normal vocal fold mobility and mucosa; her initial VRQOL score was unavailable for review.

PATIENT 3

Patient 3 was a 55-year-old teacher with a 30-year history of chronic cough. Her medical history was significant for laparoscopic fundoplication for reflux disease, seasonal allergies, and asthma. Previous treatment included proton pump inhibitors, albuterol, mucolytics, cough suppressants, and speech therapy. Her chief complaint was a chronic cough that interfered with her quality of life. Physical examination results were nonfocal, with a normal laryngoscopy result that did not reveal any laryngeal disease. Her initial VRQOL score was 21.

PATIENT 4

Patient 4 was a 41-year-old woman with a 2-year history of chronic cough, despite reflux and asthma treatments. She was a nonsmoker and nondrinker with no other significant medical history. The main reason for her office visit was social embarrassment, causing her to avoid dating and other social activities. Previous treatment with proton pump inhibitors, mucolytics, cough suppressants, and speech therapy provided no relief of her symptoms. Physical examination revealed normal laryngeal function and no pathological findings. Her initial VRQOL score was 73.

RESULTS

Of the 4 patients, 3 (75%) were women, and the mean patient age was 55.6 years (age range, 38-64 years). All 4 pa-

tients had significant relief of cough after BtxA injection. The median number of BtxA injections was 7 (range, 4-16), and the mean amount of BtxA injected was 4.0 U (range, 1.0-10.0 U) per session. The mean duration of therapy was 25.7 months (range, 7.2-42.9 months) before complete symptom resolution (**Table**).

PATIENT 1

Patient 1 was treated with electromyography-guided percutaneous injection of BtxA to the bilateral thyroarytenoid muscles. Breathiness was a mild, although not unexpected, adverse effect after treatment and without dyspnea or aspiration. His symptoms improved significantly, and he subsequently received unilateral injections to the thyroarytenoid muscles, which did not cause breathiness in his voice while relieving his chronic cough. He is now able to participate in social interactions, and his VRQOL score increased from 20 to 80 after treatment. The patient's chronic cough resolved after 16 treatments for 39.7 months without any major complications, and he has remained symptom free.

PATIENT 2

Patient 2 underwent electromyography-guided percutaneous BtxA injections to the bilateral thyroarytenoid muscles. This treatment resolved her chronic cough without any complications. The patient required 4 injections for 7.2 months before her chronic cough completely resolved, and she has been asymptomatic since then. Her VQROL scores were unavailable.

PATIENT 3

Patient 3 received percutaneous electromyography-guided BtxA injections to alternating thyroarytenoid muscles and had significant improvement with minimal voice-related adverse effects. Her VRQOL score increased from 21 to 31, and she required 6 injections for 12.9 months before her chronic cough resolved without any complications.

PATIENT 4

Patient 4 received 8 BtxA injections with electromyography guidance to achieve complete resolution of her chronic cough. She reported that the elimination of her cough had significantly improved her quality of life even though her VRQOL score decreased from 73 to 48 after treatment because of the breathiness in her voice. She wrote in her survey that despite these voice changes, "Botox has been wonderful for me and the cough. It made me stop coughing. . . . It's given me a lot of relief." She is now able to interact socially and date again. She received 8 injections for 42.9 months and has been symptom free with no reported complications.

Table. Botulinum Toxin Type A Injection for Chronic Cough Case Series[a]

Patient No./ Sex/Age, y	No. of Injections	Mean No. of Units Injected (Range)	Duration of Botulinum Toxin Type A Injections, mo
1/M/64	16	4.34 (1.00-5.00)	39.7
2/F/38	4	2.38 (2.00-2.50)	7.2
3/F/55	6	6.00 (2.50-10.00)	12.9
4/F/41	8	2.75 (2.00-3.00)	42.9

[a] All injections were made into the thyroarytenoid muscle.

COMMENT

Coughing is an essential reflex that protects the aerodigestive tract. The cough reflex is a neurologic pathway that involves stimuli activating sensory receptors, an afferent signal, integration in the brainstem and cerebral cortex, and coordinated motor actions sent through various efferent pathways. There are several possible models to explain chronic cough. Laryngeal causes of chronic cough include gastroesophageal reflux disease, emotional distress, vocal misuse, postviral cranial neuropathy, PVFM,[1] and ILS.[8] However, the common mechanism for these etiologies is a hyperfunctional larynx owing to neuroplastic changes in the brainstem[1,8] that control the cough reflex. The response to BtxA in our case series is consistent with this neuroplastic model of chronic cough. We discuss the mechanisms of cough and pharmacologic activity of BtxA as a potential treatment of neuropathic chronic cough.

There are a multitude of stimulants that can trigger cough[1-5] and at least 5 different vagal intraepithelial sensory receptors, the most important being rapidly adapting stretch receptors (RARs) and bronchial C-fiber receptors. The C fibers can cause neurogenic inflammation, which can result in the RARs enhancing the strength of the cough reflex. The larynx is dominated by mechanosensitive receptors, whereas the distal airway and bronchus are dominated by chemosensitive receptors.[1]

Activation of these receptors causes release of neuropeptides, including a group of tachykinins, such as substance P, neurokinin A, and calcitonin gene-related peptide.[1] These neuropeptides cause neurogenic inflammation.[1] Their role in cough is illustrated by cough caused by angiotensin-converting enzyme inhibitors, which prevent the breakdown of tachykinins, bradykinin, and substance P.[1,10-12] A relationship is thought to exist between neurogenic inflammation and hyperresponsiveness in the airway, which serves as a possible trigger for cough-variant asthma and chronic cough.[1,13]

The afferent input of cough is mediated by the sensory branch of the vagus nerve, which innervates various structures of the aerodigestive tract. This includes the Arnold nerve from the ear canal, pharyngeal branches, superior laryngeal branches, pulmonary branches, gastric branches from the stomach, and cardiac, diaphragmatic, and esophageal branches.[1] These inputs are received in the brainstem at the level of the nucleus tractus solitarius.[1,14] The cough center in the brainstem is also influenced by voluntary cortical input because the cough reflex can be intentionally diminished. The efferent pathway of cough begins with motor information coordinated from the cerebral cortex and cerebellum, as well as the nucleus ambiguus,[1]

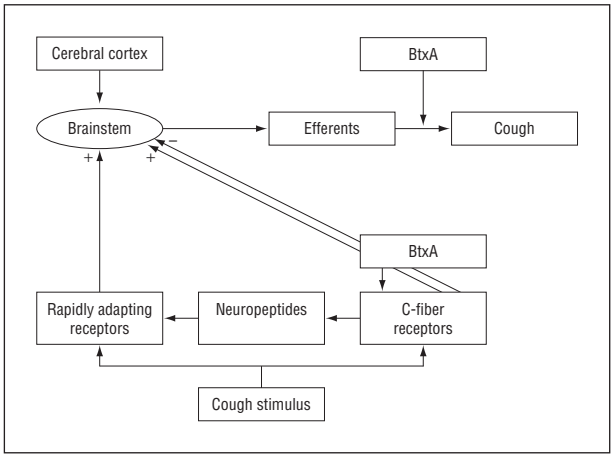

Figure. Neurophysiology of cough reflex. BtxA indicates botulinum toxin type A; plus sign, excitatory; minus sign, inhibitory.

to produce the sequential events of a cough via the recurrent laryngeal nerve (**Figure**).

There are several well-described models for chronic cough, including ILS,[3,8] PVFM,[3,6] sensory laryngeal neuropathic cough,[15] and postviral vagal neuropathy.[4] Morrison et al[8] describe ILS as a neural plastic change to brainstem laryngeal control causing a hyperfunctional larynx, resulting in voice changes, laryngeal spasms, pain, fatigue, globus, and cough. They proposed treatment modalities based on likely etiologies, such as behavioral therapy for psychogenic causes, breathing treatments for pulmonary and asthmatic causes, BtxA for neurologic and dystonia causes, and antireflux medication for chemical causes.[8] Cukier-Blaj et al[6] proposed a sensory motor laryngeal disorder to explain PVFM as a spectrum of diseases that manifest as a variety of clinical symptoms, including cough. They report laryngeal irritation caused by reflux decreases laryngeal sensitivity and results in a compensatory motor response with hyperadduction of the vocal folds during inspiration, cough, and dysphonia. They propose an inflammatory and neurogenic basis of PVFM.[6] Bastian et al[15] reported a sensory neuropathic model for chronic cough. They suggested the criteria to diagnose neuropathic cough as an idiopathic chronic cough, persistent irritable cervical and laryngeal sensations, spontaneously occurring or with specific triggers, and a nonproductive cough, with exclusion criteria based on malingering, secondary gain, abrupt onset or resolution, or periods of complete resolution. Rees et al[5] describe postviral vagal neuropathy as another model of chronic cough that is similar to other cranial neuropathies, such as Bell palsy, trigeminal neuralgia, glossopharyngeal neuralgia, and postherpetic neuralgia. They report that sensory and motor branches of the vagus nerve may be affected to cause dysphonia, vocal fatigue, paresis, pain, globus, laryngospasm, PVFM, and cough.[4,5] A common cause in these proposed models of chronic cough is neuroplasticity or central neuron adaptation to a stimulus or efferent signal causing a hyperexcitable sensorimotor state.[5] The successful treatment of chronic cough with gabapentin, amitriptyline, BtxA, and behavioral therapy also supports such a neuropathic model for the pathophysiology of chronic cough.

We also report a neuropathic model for chronic cough. We believe that a change in the central nervous system likely causes the sensory and motor pathways of cough to be in a hyperexcitable state.[5] This neural plasticity can lower the threshold for cough stimulation and increase laryngeal tone. These changes are mediated through new axonal connections or changes in gene expression.[5] Altered sensorimotor pathways are well documented in gustatory sweating, gustatory epiphora, and chronic neuropathic pain,[16,17] all of which have been successfully treated with BtxA. This neuroplastic model of cough is also supported by postviral vagal neuropathy.[1,4,5,9] Review of patient history often reveals a previous upper respiratory tract infection, as seen in patient 1, which may alter the cough reflex. Other examples of virus-induced neuropathies also support this theory, such as postherpetic neuralgia, human immunodeficiency virus neuropathy, and Guillain-Barré syndrome.[1] Postviral neuropathy is thought to be caused by either direct infection of the nerve or an inflammatory response involving the nerve.[1,4,5] For chronic cough, the presumptive nerve injury would be cholinergic receptors of the vagus nerve, causing changes in cough threshold and airway hyperactivity.[1]

It is also postulated that repeated noxious stimuli cause release of neurotransmitters. Prolonged sensory disturbances associated with tissue injury are thought to result from reduction in nociceptor threshold, reduced inhibitory control, or increased excitability of central nervous system neurons. C-fiber neuropeptides and excitatory amino acid neurotransmitters are thought to contribute to these changes in central nervous system function[1] (Figure). Chronic cough produces a harsh glottic closure and vocal fold trauma with each cough. This repetitive trauma produces repeated release of neuropeptides and contributes to the feedback loop.

Botulinum toxin type A is a potent neurotoxin produced by the anaerobic bacterium *Clostridium botulinum*. There are 7 serotypes of the toxin based on immunologic specificity, labeled types A through G.[18] Botulinum toxin inhibits calcium-dependent release of acetylcholine chloride at the presynaptic neuromuscular junction and causes local paralysis in a dose-dependent fashion until new nerve terminals are regenerated.[18] Botulinum toxin can also act by inhibiting neurologic signaling markers, such as substance P, glutamate, and modulate sensory feedback loops.[19] This is illustrated in its use for hyperhidrosis and gustatory sweating, in which botulinum toxin inhibits release of acetylcholine from sympathetic nerves innervating eccrine sweat glands and salivary glands.[20] However, the only Food and Drug Administration–approved uses for BtxA are for blepharospasm, strabismus, hyperhidrosis, glabellar rhytids, and cervical dystonias.[18]

In several off-label uses of BtxA for focal muscle dystonia, it was incidentally noted that BtxA produced pain relief before muscle decontraction,[21] prompting investigators to explore its analgesic properties. Off-label uses were also encouraged by in vitro studies that showed BtxA could inhibit neurogenic inflammation by attenuating the release of neuropeptides (eg, substance P, calcitonin gene-related peptide, and glutamate) from C-fiber receptors.[21] However, other reports[22] suggest that BtxA has minimal effect on pain on skin despite decreasing neurogenic

inflammation. These results indicate that BtxA may have a selective effect on pathological pain, and Ranoux et al[21] hypothesize that BtxA may have a greater effect on sensitized pain fibers by binding to nociceptive receptors with more affinity in patients with chronic neuropathic pain compared with patients with acute pain or that another unknown central nervous system target was involved. They also reported that patients showed improved pain relief over time after 1-time injection of BtxA, suggesting a change in neural plasticity and alteration of pain thresholds in chronic neuropathic pain. As in our case series, many patients had significant relief of their cough before the expected onset of muscle paresis caused by BtxA, which also suggests an effect on sensory and possible neurogenic inflammatory pathways.

Krämer et al[22] reported that BtxA reduced neurogenic inflammation but only marginally reduced cutaneous pain in otherwise healthy volunteers. However, this finding is consistent with the ability of BtxA to selectively treat neurologic disease mediated through neuropeptides, such as chronic neuropathic pain and chronic cough, instead of acute pain pathways. Krämer et al[22] and Nichols et al[23] speculated that release of neuropeptides from peripheral C fibers would cause vasodilation and neurogenic inflammation, but the neuropeptides in the spinal cord and central nerves induce central nociceptive sensitization. These studies demonstrated that BtxA was effective in decreasing vasodilation and neurogenic inflammation in cutaneous skin but did not test the effects of BtxA on central nerves.

We also speculate that injecting BtxA in the thyroarytenoid muscles acts on both sensory and motor components of laryngeal neuropathy and chronic cough by reducing laryngeal hypertonicity through muscle paresis and diminishing the severity of trauma from repeated coughing. However, symptom relief occurred before the expected paralytic effects of botulinum toxin on laryngeal musculature, suggesting another mechanism of action of BtxA on neuropathic chronic cough, as described by Ranoux et al[21] and Krämer et al.[22] Botulinum toxin type A likely selectively affects chronic neuropathic pathways instead of acute pain pathways by decreasing neuropeptide-mediated neurogenic inflammation and interrupting the feedback cycle, allowing the larynx to regain baseline sensitivity to stimuli and decrease the exaggerated laryngeal response to cough stimuli.

The limits of this study are the small sample size and retrospective methods. However, to our knowledge, we report the first experience of BtxA injections used to treat chronic cough in adults and hope to encourage further discussion and investigation of the pathophysiology of cough.

The mechanisms of neural plasticity and a neuropathic model of chronic pain provide valuable insight into chronic cough. The neuropathic model of chronic cough is consistent with ILS, postviral vagal neuropathy, PVFM, and other neuropathic models, where neural plastic changes cause hyperkinetic laryngeal dysfunction.[8] It also shares similarities with chronic neuropathic pain disorders. The successful treatment with BtxA for chronic pain and chronic cough also supports a neuropathic model.[7,23] It has been reported that BtxA is effective in reducing neurogenic inflammation and possibly modulating central nociceptive feedback.[18,19] We believe that BtxA works on neuromuscular junctions to decrease the strength of cough and severity of repeated glottic trauma by altering motor pathways and reducing neuropeptide release and neurogenic inflammation in afferent sensory pathways to treat chronic cough.

Further research is warranted to study the analgesic properties of BtxA and its ability to reduce neurogenic inflammation in chronic neuropathies. Our report suggests that BtxA may be considered a possible treatment option for chronic cough after thorough workup fails to find a treatable diagnosis and empirical treatment of the most common causes of chronic cough are unsuccessful. Other neuropathic medications have been reported to treat chronic cough, such as gabapentin and amitriptyline, but they are also not without risks or adverse effects, such as sedation, anticholinergic effects, dizziness, and postural hypotension. Botulinum toxin type A injection is an invasive procedure, but it is safe and effective and caused no major complications in our study. It can also be performed in the office setting. Some patients reported temporary breathiness and mild pain with injection of BtxA. After an average of 9 sessions during a mean span of 25.7 months, patients were successfully treated and had complete resolution of their chronic cough.

In conclusion, we report our early experience of treating chronic cough with BtxA to support the neuropathic model for chronic cough caused by neuroplastic changes and laryngeal hyperactivity. Botulinum toxin type A was effective against both motor and sensory components of the laryngeal neuropathy of chronic cough by directly decreasing laryngeal hypertonicity and possibly reducing neurogenic inflammation and neuropeptide-mediated cough. Botulinum toxin type A can be successfully used to treat chronic cough refractory to other medical therapies.

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Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Lieser and Sinacori. *Acquisition of data:* Chu, Lieser, and Sinacori. *Analysis and interpretation of data:* Chu and Sinacori. *Drafting of the manuscript:* Chu and Lieser. *Critical revision of the manuscript for important intellectual content:* Lieser and Sinacori. *Statistical analysis:* Chu. *Administrative, technical, and material support:* Chu and Lieser. *Study supervision:* Lieser and Sinacori.
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Correction

Error in Byline. In the byline of Radiology Quiz Case 1, which appeared in the May 2009 issue of the *Archives* (2009;135[5]:516), the first author's first name should have been spelled Navneet.