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CLINICAL RECORD

Cough after laryngeal herpes zoster: a new aspect of post-herpetic sensory disturbance

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Abstract

Objective: Although neurogenic cough is increasingly recognised, its pathophysiology remains obscure. We describe two cases of chronic cough following laryngeal herpes zoster, a rarely described manifestation of varicella-zoster virus reactivation, and suggest that this may be analogous to post-herpetic neuralgia. The same mechanisms may cause both phenomena.

Case reports: We describe two cases of chronic cough persisting for more than three months following an acute attack of laryngeal herpes zoster.

Conclusion: Neuronal damage by varicella-zoster virus results in irritable nociceptors and deafferentation, mechanisms known to cause post-herpetic neuralgia. When the vagus nerve is affected, as in laryngeal herpes zoster, the result may be a chronic cough. Similar damage may underlie chronic neurogenic cough in other contexts.

Key words: Herpes Zoster; Laryngeal Diseases; Vagus Nerve Diseases; Cough; Neuralgia, Postherpetic

Introduction

Herpes zoster represents a reactivation of varicella-zoster virus dormant in sensory nerve ganglia after acute infection. Typically, it presents with vesicular eruptions in the skin of the affected dermatome. Neurogenic sequelae, particularly pain, are well documented. Mucosal manifestations of herpes zoster are rarely reported and vagal nerve manifestations still more so.

We describe two cases of vagal nerve herpes zoster with characteristic presentations and clinical courses. Both developed cough as a post-herpetic sequela, an aspect heretofore not described. We follow this with a discussion on the proposed pathophysiology of this phenomenon, likening it to the more common post-herpetic neuralgia.

Case reports

Patient one

A 66-year-old female smoker complained of six days of hoarseness, progressive odynophagia and intense, unilateral throat pain. Flexible, transnasal laryngoscopy revealed numerous ulcers with purulent exudate on the left half of the epiglottis, the left supraglottic area, and the left lateral and posterior pharyngeal wall (Figure 1). The left vocal fold was markedly oedematous, but vocal fold mobility was intact bilaterally. An empirical diagnosis of laryngeal zoster was made based on examination findings, and the patient was started on a 7-day course of valaciclovir.

A week later, her symptoms had largely resolved. She was able to tolerate liquids and some foods by mouth. Flexible laryngoscopy showed complete resolution of the ulcers, with some areas of patchy erythema but complete re-mucolisation. Vocal fold oedema was much reduced, and it became clear the patient had mild Reinke's oedema at baseline.

Eleven months later, she returned to the clinic complaining of easily provoked, non-productive cough and a persistent foreign body sensation since the acute episode. Rigid, peroral laryngoscopy revealed bilateral Reinke's oedema and raised the possibility of laryngopharyngeal reflux. She was advised to stop smoking and was prescribed omeprazole 40 mg daily.

Eight months later, the patient reported no improvement to her cough. She declined treatment with amitriptyline or gabapentin. She was subsequently lost to follow up.

Patient two

A 62-year-old man presented to a laryngologist in Australia with a 1-week history of left-sided, progressive throat pain, radiating to the neck and ear, with an associated feeling of a lump at the base of the tongue. Three days prior to the onset of the pain, he had noted a metallic taste on intake of food and beer. Flexible laryngoscopy showed vesicles on the left side of his pharynx, vallecula and supraglottis (Figure 2). The ear and the laryngeal and facial movements were normal. There were no motor symptoms or signs. An empirical diagnosis of herpes zoster was made. Antivirals were not prescribed as they are not funded for the treatment of herpes zoster in Australia beyond 72 hours of symptom onset.

The patient's pain increased over the next three days, with associated malaise and the development of aural fullness and

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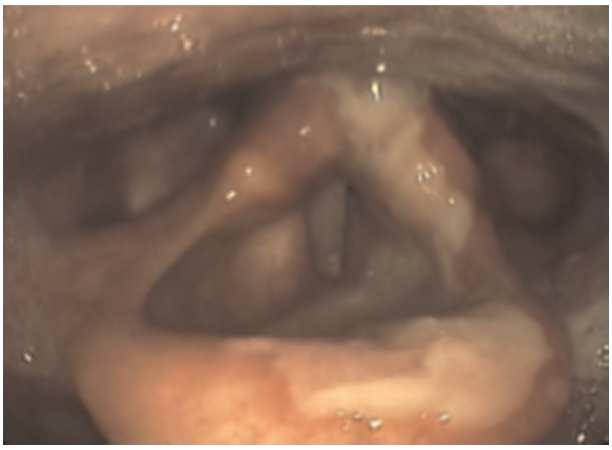

FIG. 1

Flexible, transnasal laryngoscopic view of the first patient, showing numerous ulcers with purulent exudate on the left half of the epiglottis, the left supraglottic area, and the left lateral and posterior pharyngeal wall.

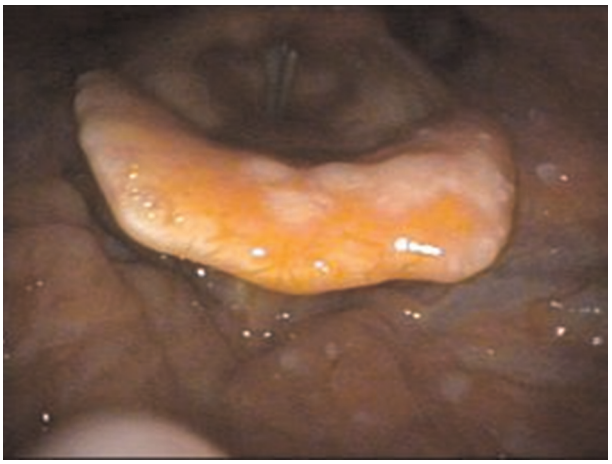

FIG. 2

Flexible, transnasal laryngoscopic view of the second patient, showing herpetic vesicles on the left supraglottis, most prominent on the left half of the epiglottis.

bloody left otorrhoea. Daily oral prednisolone 50 mg was prescribed.

Twelve days after his initial presentation, his symptoms had improved. Examination revealed ulceration of the inferior external auditory meatus and vesicles over the left tonsillar region. Swabs taken from the ear were positive for varicella-zoster virus DNA on polymerase chain reaction analysis. A throat swab was negative. Serology was also positive for varicella-zoster virus immunoglobulin G.

One month after presentation, the patient described persistent dysgeusia, and a new, debilitating cough which had started three weeks after his initial symptoms. The cough was triggered by speaking and laughing. Laryngovideostroboscopy was normal. He was treated with gabapentin which yielded partial symptomatic relief.

Review at six months found that the patient's cough was improving but he was still experiencing frequent dysgeusia, throat irritation and watering of the left eye, which triggered and was relieved by a coughing fit. Attempts to reduce the dose of gabapentin resulted in exacerbation of these symptoms.

Discussion

Laryngeal zoster is a rare manifestation of herpes zoster, known largely from case reports, and represents reactivation of latent varicella-zoster virus from ganglia. In these cases, the distribution of mucocutaneous lesions suggests a vagal origin of the eruption.

The sensory distribution of the vagus nerve includes the internal branch of the superior laryngeal nerve, which supplies the epiglottis and supraglottic area to the level of the vocal folds,[1] and the auricular branch of the vagus, which supplies part of the external auditory meatus (Figure 3).[2] The former explains the vesicular eruption in the left supraglottic area of both presented patients, while the latter explains the ulceration in the external auditory meatus of the second patient. The internal branch of the superior laryngeal nerve also carries taste sensation from the vallecula and tongue base, explaining the dysgeusia experienced by our second patient.

Following a literature review, we believe we are the first to present chronic cough as a sequela of laryngeal zoster. We searched the Medline and PubMed databases using the Medical Subject Heading key words 'herpes zoster', 'laryngeal diseases', 'vagus nerve diseases', 'cough' and 'neuralgia, postherpetic', and the additional key words 'postherpetic cough' and 'laryngeal zoster'. Twenty-five case reports were identified, published between 1972 and 2012 and describing laryngeal zoster, herpes zoster laryngitis, herpes laryngis, pharyngolaryngeal zoster and Ramsay–Hunt syndrome with dysphagia. These cases were scrutinised for reports of long-term cough following herpes zoster infection; none were found.

Chronic cough following laryngeal herpes zoster is distinct from the more commonly described post-viral vagal neuropathy,[3] both because of the characteristics of the antecedent acute illness and the absence of motor signs. We believe the cough represents neurogenic hypersensitivity, typical of some mechanisms for sensory neuropathic cough[4] and analogous to post-herpetic neuralgia, a

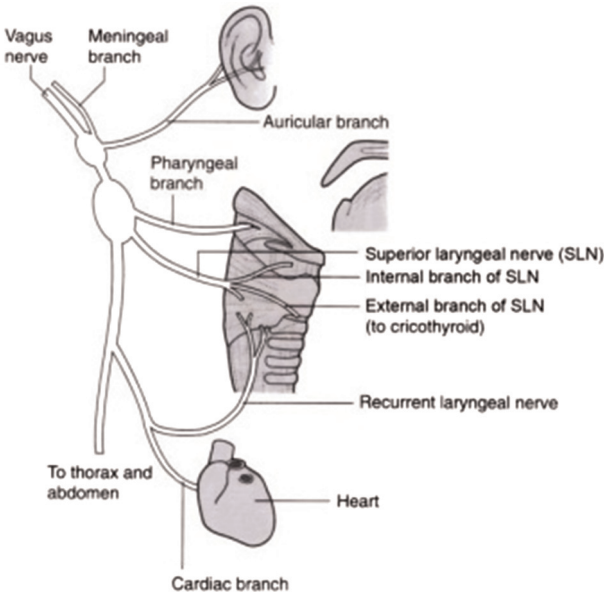

FIG. 3

Diagram of the branches of the vagus nerve in the head and neck. Adapted with permission from Elsevier (© Elsevier 2001).[2]

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common complication of dermatomal herpes zoster and one of the most common types of neuropathic pain.[5]

Post-herpetic neuralgia is dermatomal pain that persists beyond three months of the initial presentation of zoster. Fields *et al.*[5] claimed that both peripheral and central pathophysiological mechanisms contribute to this, and suggested two mechanisms: irritable nociceptors and deafferentation. Three processes give rise to irritable nociceptors. First, axonal damage from infection leads to spontaneous activity at several sites along the primary afferent. Second, axonal damage causes up-regulation of excitatory receptors in the damaged neurons. Third, inflammation anywhere along the axon can produce a hyper-excitable state. Deafferentation describes central neuron re-synapsing with an aberrant peripheral neuron as a result of deprivation of its original primary afferent due to damage. Thus, the new primary afferent, which usually responds to innocuous stimuli such as light touch, forms a connection with the pain pathway, causing the sensation of pain to be evoked erroneously, manifesting as allodynia. The varying clinical presentations of post-herpetic neuralgia, from constant or paroxysmal pain to allodynia, have been attributed to damage by herpes zoster to different nerve fibre subtypes, specifically myelinated Aβ or Aδ or unmyelinated C-fibres.[6] These fibre subtypes are also known to be part of the afferent arc of the cough reflex.[7]

In 1999, Morrison *et al.*[8] first introduced the idea of the irritable larynx, in which neuronal networks in the brainstem responsible for laryngeal control are held in a perpetual hyper-excitable state and react inappropriately to sensory stimulation. They suggested two mechanisms, which parallel those proposed by Fields *et al.*[5]: (1) the rewiring of central nervous system neurons to synapse with other first-order neurons following injury and withdrawal of the original primary afferent, similar to the deafferentation hypothesis, and (2) a change in gene regulation following repeated noxious stimulation to the point of altering the neuron's phenotype and thus response to stimulus, one of the processes which may cause an irritable 'nociceptor'.

- **Two cases of herpes zoster of the vagus nerve, resulting in chronic cough, are presented**
- **This is distinct from the more common post-viral vagal neuropathy**
- **This post-herpetic cough may be analogous to the post-herpetic neuralgia of dermatomal shingles**
- **Herpetic infection may permanently damage the vagus nerve, causing hyper-excitability, deafferentation and/or inappropriate re-synapsing**
- **Neurogenic medication (e.g. gabapentin or amitriptyline) may be effective**

Based on these cases, we propose that direct herpetic infection of the vagus nerve or its branches may leave them in a permanently damaged state due to inflammation and necrosis, leading to hyper-excitability of the injured nerve itself or rewiring of its second-order neuron in the cough reflex arc to accommodate the axon of an inappropriate primary afferent, as may happen in post-herpetic neuralgia.

While the internal branch of the superior laryngeal nerve is the main primary afferent of the cough reflex, it may not necessarily be responsible for the post-herpetic cough. Multiple sensory branches of the vagus are able to trigger the cough reflex arc.[9] Receptors have been found as far down as the pericardium and the stomach. Stimulation of Arnold's nerve may elicit cough. Our second patient's external auditory meatus ulceration indicates involvement of Arnold's nerve. The resultant neuropathy may theoretically be of any sensory branch of the vagus nerve causing referred cough.

Our two cases suggest that post-herpetic cough may occur as a direct neurological complication of laryngeal zoster, analogous to post-herpetic neuralgia in dermatomal shingles. We suggest that neurogenic medications such as gabapentin or amitriptyline be considered for patients whose cough follows an episode of laryngeal zoster and is unresponsive to other treatment. Further research would be useful in determining the prevalence of cough in patients who have had laryngeal zoster.

Conclusion

This report presents two cases of herpes zoster of the vagus nerve resulting in chronic cough, as distinct from the more commonly described post-viral vagal neuropathy. We believe that this post-herpetic cough is analogous to the post-herpetic neuralgia seen in cases of dermatomal shingles. Herpetic infection may permanently damage the vagus nerve, causing hyper-excitability or deafferentation and inappropriate re-synapsing within the cough reflex arc.

Neurogenic medications such as gabapentin or amitriptyline may be considered for these patients.

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