CLINICAL VIGNETTE

Chronic Refractory Cough Associated with COVID-19 Infection

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Case Report

A 43-year-old female presented for pulmonary consultation for severe cough. Three weeks prior she developed a productive cough with low grade fever, fatigue and dyspnea with positive COVID-19 PCR (Polymerase Chain Reaction) test. Other concurrent symptoms included loss of taste and smell as well as mild diarrhea.

Evaluation at the local emergency room revealed a normal chest radiograph. C reactive protein was mildly elevated at .59 mg/dl (normal < .49 mg/dl). Ambulatory oximetry on room air revealed a nadir of 94%. She was prescribed benzonatate for cough suppression, an albuterol inhaler for mild wheezing and discharged to home isolation.

Initial follow-up with primary care revealed resolution of fever and gastrointestinal symptoms. Her cough persisted with increased severity at night, interfering with sleep. Cold air exposure exacerbated the cough. Albuterol, provided transient relief and addition of fluticasone-salmeterol inhaler was ineffective.

Past medical history was only notable for remote cholecystectomy. There was no history of asthma, gastroesophageal reflux, or allergic rhinitis. The patient is a lifelong nonsmoker.

Physical examination was notable for mild wheezing. Cardiac examination was unremarkable except for resting tachycardia of 100 beats/min.

Laboratory data included normal CBC, BNP, sedimentation rate, C reactive protein, IgE, and CPK.

The patient was started on prednisone 40 mg daily for 5 days as well as nebulized budesonide 0.5 mg twice daily in addition to albuterol. She had no improvement with corticosteroids, with short term relief with albuterol, but worsening tachycardia after use, in the 130's on self-monitored pulse oximetry. EKG showed sinus tachycardia without evidence of ischemia or ectopy.

Due to persistent resting tachycardia and dyspnea the patient had a CT (Computed Tomography) pulmonary angiogram with no evidence of pulmonary embolism. There were no parenchymal infiltrates. Holter monitor showed no other dysrhythmias. Transthoracic echocardiogram revealed mild global hypokinesis with an ejection fraction of 45-50%. Cardiology stated the findings were compatible with COVID-19 myocarditis, and she was started on sacubitril/valsartan and metoprolol.

Despite the interventions, the severe coughing paroxysms persisted and resulted in emesis as well as hoarseness. Narcotic antitussives provided partial relief, with no benefit from oral proton pump inhibitors or tiotropium bromide inhalation.

Gabapentin trial improved cough and the dose was gradually titrated to 700 mg daily in divided doses with approximate 75% improvement in symptoms. Further increases were limited by neurocognitive impairment.

Head and Neck consultation performed fiberoptic swallowing examination, which was unremarkable. Laryngovideostroboscopy demonstrated mild restriction of mucosal wave bilaterally. She underwent right superior laryngeal nerve block with lidocaine and triamcinolone. Amitriptyline 25 mg was started at bedtime. She was referred to speech therapy to improve laryngeal strength and voice quality.

Discussion

Cough during the COVID-19 pandemic is one of the most distressing symptoms due to both medical and social implications during these unprecedented times. Early data in the pandemic suggested that cough was only the fourth most prevalent symptom at 28% of patients hospitalized for COVID-19. Fever (75.5%), dyspnea (31.8%) and myalgias (31.7%) were more common.[1] Cough, however, is far more easily recognized. This causes increased anxiety to both patients and the public. In patients with Post COVID Syndrome, or "long haul COVID," cough was present in only 2.5% surveyed patients one year after hospitalization.[2] It is the most common symptoms in patients that seek pulmonary evaluation.

Acute cough has been defined as lasting 3 weeks or less. Subacute cough and chronic cough have last between 3-8 weeks and greater than 8 weeks, respectively.[3]

Standard evaluation should include assessment of the more common etiologies of chronic cough including asthma, allergic or non-allergic chronic rhinitis, and gastroesophageal reflux due to the high probability of multifactorial causes contributing to this symptom complex.

Chronic COVID-19 related cough is different from many upper respiratory viral infections is that it is most often associated with fatigue, dyspnea, and chest pain associated with Post COVID-19 syndrome. Non COVID-19 viral infections associated with cough are felt to be due to upper respiratory tract inflammation and airways reactivity.[4] The associated symptoms of Post COVID-19 syndrome including loss of taste and smell, fatigue, and chest pain points to possible neurogenic derangement of both peripheral sensory nerves and the central nervous system (I.e., "brain fog").[4]

The cough reflex involves stimulation of sensory peripheral nerves to the Vagus nerve and subsequently to the brainstem. One postulated cause is sensory nerve infection causing neuroinflammation and neuroimmune reaction leading to hypersensitivity of the cough reflex.[5]

This postulated etiology would explain the benefit of neuromodulation drugs such as gabapentin and amitriptyline in chronic cough, although limited in part due to neurocognitive effects at higher dosages.[6,7]

Antimuscarinic agents such as tiotropium bromide have been shown to reduce post viral cough hypersensitivity.[8]

Head and Neck surgeons have long attributed chronic cough having a neuro-hypersensitivity etiology. Laryngovideostroboscopy can reveal vocal cord fold movement abnormalities that are associated with neuropathy/neuroinflammation involving the superior laryngeal nerve. Nerve block with lidocaine with corticosteroids has been shown effective in chronic cough associated with vocal fold dyskinesis.[9,10]

Injection of botulinum toxin A (Botox) into the thyroarytenoid muscle weakens the adductor muscle to decrease the severity of the cough reflex. Botox has also been shown to reduce release of substance P and other neurotransmitters thought to be important in the cough reflex.[11]

Summary

The stigma of post COVID-19 cough amplifies both physical and mental stress associated with the pandemic, particularly associated with other symptoms in the Post COVID-19 Syndrome. It is also refractory to standard treatments for chronic cough due to non-COVID etiologies such as cough suppressants, bronchodilators, and anti-reflux therapy. Our patient's refractory cough suggested a neuropathic etiology and improved significantly with neuromodulator drugs. Laryngeal hypersensitivity demonstrated by laryngovideostroboscopy allowed further improvement in cough after superior laryngeal nerve block was performed when neuromodulator therapy could not be increased due to depression of cognition. The patient is currently being considered for botulinum toxin A injection.

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