Grand Rounds Review

Drug-Induced Paradoxical Vocal Fold Motion

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Vocal cord dysfunction, also known as paradoxical vocal fold motion (PVFM), is a disorder characterized by abnormal vocal cord adduction during inspiration. PVFM is commonly misdiagnosed as asthma because of the similarity of symptoms: cough, wheezing, chest pain, and dyspnea. We present the clinical vignette of a 36-year-old woman with juvenile rheumatoid arthritis and multiple adverse drug reactions who presented with recurrent episodes of unrecognized PVFM during skin testing for drug allergy, omalizumab treatment, and tocilizumab desensitization. Before the diagnosis of PVFM, these episodes were treated as anaphylaxis, including the administration of epinephrine. Once diagnosed and treated for PVFM, the patient did not present any further events and continued treatment for drug allergy. PVFM may be underreported in hypersensitivity reactions because of the similarity to Type 1-mediated respiratory symptoms and comorbid asthma. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

Key words: *Anaphylaxis; Adverse drug reaction; Drug hypersensitivity; Vocal cord dysfunction; Paradoxical vocal fold motion; Desensitization*

CASE REPORT

A 36-year-old woman with asthma, gastroesophageal reflux disease, generalized anxiety disorder, rheumatoid arthritis, and chronic idiopathic urticaria (with daily intake of up to 200 mg of diphenhydramine per day) had adverse reactions to 15 different medications, including 7 that reportedly induced anaphylaxis, shortness of breath, and/or throat symptoms (Table I). The patient had a history of 15 emergency department (ED) visits in 2016 alone, and she frequently received epinephrine because of concern for anaphylaxis (Table I and Figure 1). She was initially evaluated in the allergy clinic for possible hypersensitivity to tocilizumab after she developed dyspnea during an infusion of this agent for the treatment of rheumatoid arthritis. As she had positive skin testing to tocilizumab at the second intradermal level (20 mg/mL), tocilizumab desensitization was recommended. Despite desensitization, she continued to present with severe inspiratory stridor during infusion, and she received epinephrine for this on multiple occasions. She had similar symptoms during her initial omalizumab injection and during skin testing to mepivacaine, resulting in a code being called and in the administration of epinephrine during each episode (Figure 1). Her predominant symptoms during these events were severe stridor, dyspnea, gagging, hoarseness, and difficulty speaking, all without documented vital sign changes (Figure 1). Importantly, on physical examination during her acute reaction to local anesthetic skin testing (mepivacaine), she had stridor but no wheezing. She had a transient loss or impairment of consciousness twice, during which time the stridor completely resolved, only to recur when she regained full consciousness. Her local anesthetic skin test areas were completely negative for any wheal or flare reaction. She was transferred to the ED, and visualization of the upper airway was attempted, but she could not tolerate this procedure.

Through repeated observation of the patient during reaction episodes, it became clear that she was presenting with a rapidly reversible process without mucocutaneous signs or symptoms, repeatedly negative serum tryptase, and an absence of mast cell activation that was inconsistent with true anaphylaxis. The time course of the development, resolution, and redevelopment of symptoms suggested a primary neurological or neuromuscular process. Using stridor as the guiding central symptom, and seeing its rapid resolution with loss of consciousness, paradoxical vocal fold motion (PVFM) was suggested as an alternative diagnosis. Evaluation by otolaryngology confirmed this diagnosis by direct visualization of the upper airway (see Video 1, available in this article's Online Repository at www.jaci-inpractice.org). The patient received speech therapy focusing on respiratory control of PVFM. The patient did not receive continuous psychiatric care.

The patient underwent 6 standard tocilizumab desensitizations without adverse reaction after speech therapy. She responded so well to treatment that her antihistamine premedication dose was lowered, and the dose of tocilizumab was increased to improve control of her rheumatoid arthritis. The patient discontinued daily antihistamines, and has not received epinephrine in the 5 months since the diagnosis and management of PVFM (Figure 1). In addition to decreasing the

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Abbreviations used
ACE- Angiotensin converting enzyme
CT- Computed tomography
ED- Emergency department
EI PVFM- Exercise-induced paradoxical vocal fold motion
ICU- Intensive care unit
PVFM- Paradoxical vocal fold motion

premedication doses, the resolution of the patient's previous reliance lorazepam is reflective of the success of speech therapy.

INTRODUCTION

PVFM is characterized by paradoxical vocal cord adduction during inspiration. Two distinct phenotypes of PVFM have been postulated: exercise-induced PVFM (EI PVFM) and sudden onset PVFM.[1] EI PVFM has a clear trigger (exercise), whereas the triggers for sudden onset PVFM are not well defined.[1] Although the precise etiology of PVFM is unknown, the incidence is higher among women than men (2 to 3:1) and PVFM is associated with comorbidities including gastroesophageal reflux disease, irritable bowel syndrome, and psychiatric diagnoses.[2,3] PVFM may be underreported in hypersensitivity reactions because of the similarity to Type 1-mediated respiratory symptoms and comorbid asthma.[4] PVFM is commonly misdiagnosed as asthma because of the similarity of symptoms, namely cough, wheezing, chest pain, and dyspnea.[2,4] Therefore, PVFM can be difficult to identify as the primary culprit during an acute drug hypersensitivity reaction, resulting in misdiagnosis, over usage of medical resources, and increased health care costs.[2,4,5] PVFM presents mostly during inspiration, but expiratory PVFM has been described as well, with exaggerated adduction of vocal cords during expiration. Acute episodes of PVFM can result in endotracheal intubation for presumed severe upper airway obstruction, as patients present with stridor, hoarseness, tachypnea, chest tightness, and shortness of breath.[3,6-9] Appropriate treatment of PVFM during an episode includes recognition of the condition, reassurance that the condition is self-limiting, and sedation with benzodiazepines, whereas long-term treatment includes management of underlying comorbidities, which may be triggers, as well as speech and behavioral therapy.[1,2,10]

ETIOLOGY AND CLINICAL PRESENTATION

Etiology

Originally, PVFM was thought to be psychological in nature, with stress and anxiety as the main triggers. Currently, it is considered a functional disorder that may relate to the role of glottic closure in protecting the trachea and lungs.[5-7] The exact mechanisms of PVFM remain unknown; however, the proposed mechanisms include altered autonomic input from central brain regions resulting in laryngeal hyperresponsiveness, other changes in brainstem laryngeal control, motor neuropathy, and inflammation and irritation of the vocal cords from processes such as gastroesophageal reflux.[3,6,8-11] Most patients have associated medical conditions that can also be acute triggers. These include asthma, hyperventilation, exposure to tobacco smoke, allergic laryngitis, viral infection, untreated sleep apnea, gastroesophageal reflux disease, and rhinitis.[3,8,12-15]

TABLE I. Drug allergies

Drug	Reaction
Bupivacaine*	Shortness of breath, stridor, difficulty speaking, and swallowing, SVS
Ceftriaxone*	Cough, respiratory distress, SVS
Gadolinium-containing contrast media	Angioedema
Morphine	Shortness of breath, rash
Penicillins	Rash
Sumatriptan	Shortness of breath
Tocilizumab*	Shortness of breath, SVS
Divalproex sodium	Hives, throat itchiness
Isoniazid	Rash
Lidocaine	Rash
Metoclopramide	Akathisia
Latex	Rash
Prochlorperazine	Akathisia
Omalizumab	Nasal congestion, shortness of breath, difficulty speaking
Mepivacaine*	Throat itching, stridor, and difficulty speaking, coughing, gagging, SVS

SVS, Stable vital signs.
*Listed as anaphylaxis in the electronic medical record.

Clinical presentation

Episodes of PVFM typically present abruptly and last from seconds to minutes, but have been reported to last longer. Symptoms resemble other causes of upper airway obstruction such as laryngeal angioedema, and include cough, choking, and dyspnea, but without other clinical signs of a true allergic reaction (such as accompanying urticaria).[6,8,16,17] Patients often report feelings of throat tightness, and have greater difficulty with inhalation than exhalation, but have no response to rapid acting bronchodilators. The hallmark physical findings include audible stridor, respiratory distress with accessory muscle use, inability or difficulty speaking, hoarseness, and voice change.[12,18] Vital signs are typically stable, without hypoxemia, and dyspnea appears and resolves more rapidly in PVFM than in asthma. Loss of consciousness has been reported with PVFM, but whether there was resolution of stridor during loss of consciousness has not been previously reported.[19,20] Careful auscultation of the neck and lungs allows the clinician to differentiate PVFM's stridor from the true wheezing of asthma. Commonly reported triggers include perfumes, odors, changes in humidity and/or temperature, exposure to chemicals, and strong emotions.[17,18] Patients typically have multiple ED visits and/or intensive care unit (ICU) admissions, and some have a concomitant diagnosis of asthma or idiopathic allergic reactions.[10,21-23] The presence of a tracheostomy scar or a history of intubation does not exclude a diagnosis of PVFM.[6]

DIAGNOSIS

Transnasal laryngoscopy is key to visualizing vocal cord movement and rapidly ruling out other upper airway pathology. However, laryngoscopy often occurs when patients are asymptomatic.[6] During an active episode of PVFM, there is narrowing on inspiration as well as marked narrowing on exhalation with