CASE PRESENTATION: A 31-year-old woman (gravida 3 and para 1-0-1-1 at 20 weeks gestation) was admitted to the hospital for a presumed acute asthma exacerbation. She had a history of severe persistent asthma since childhood. She described her symptoms as progressively worsening since the beginning of her pregnancy. In addition to her dyspnea and wheeze, both of which occurred at rest and with exertion, she complained of worsening hoarseness and mild dysphagia of solid foods over the week before admission. Her primary care provider treated her with a combined corticosteroid and long-acting beta-agonist inhaler, albuterol inhaler and nebulizer, azithromycin, and two courses of prednisone without improvement. Her allergist performed a handheld spirometry 2 months before admission in the office. She had a social history of alcohol dependence but had been sober for 9 months. She was a former one-pack-per-day smoker but quit 20 weeks before admission and used marijuana occasionally. She had no known occupational or inhalation exposures.

Physical Examination Findings
On presentation, she was ill-appearing with mild tachycardia and oxygen saturation of 98% on 2 L/min via nasal cannula. Examination of her lungs revealed the following: retraction of her neck muscles during inspiration, diminished air entry with wheezes in the upper lung fields, and prolonged expiratory phase. Wheezes were louder on auscultation over the central airways (neck) compared with the upper lung fields. Vocal hoarseness and stridor were present and worsened throughout the interview. Her posterior pharynx was clear, with no palpable neck masses or lymphadenopathy. She would intermittently be in tripod position to breathe and was only able to speak in two- to three-word sentences, because her voice would terminate abruptly while she was speaking.

Diagnostic Studies
Office handheld spirometry that had been completed by her allergist revealed moderate airway obstruction with the expiratory flow-volume loop depicted in Figure 1A. Repeat spirometry 3 weeks later demonstrated FEV₁ of 1.21 L (39% predicted), FEV₁/FVC of 52, with no significant improvement after the bronchodilator. The expiratory flow-volume loop showed flattening of the curve (Fig 1B).

CBC count showed normal WBC and eosinophil counts. Electrolytes were also normal. COVID-19 and influenza A/B RNA were not detected. A chest
radiograph that was obtained in the ED did not show any acute cardiopulmonary abnormalities (Fig 2).

The patient did not improve with conventional treatment for asthma exacerbation. The Pulmonology Department was consulted, and they recommended evaluation by the Otolaryngology Department. Per the Otolaryngology Department recommendations, a noncontrasted CT of her neck was ordered, and it revealed a right laryngeal mass that measured 3.1 × 2.1 × 2.2 cm, extending from the aryepiglottic fold cranially to the right subglottic region probably centered in the false cord (Fig 3A–C).

The Otolaryngology Department performed laryngoscopy and biopsy of the mass. Intraoperative findings included a large, lobular, transglottic lesion on the right side with a firm, fixed right vocal cord that extended up to the anterior commissure but did not involve the right arytenoid. There was no infraglottic spread, and the pyriform sinuses and vallecula were uninvolved. A biopsy specimen was obtained for histopathology evaluation. It showed nests of nonkeratinizing ovoid cells with hyperchromatic nuclei, indistinct borders, and p16 stain positivity. (Fig 4).
What is the diagnosis?
Diagnosis: Human papilloma virus (HPV)-related squamous cell carcinoma of the larynx that was causing asthma-like symptoms

Discussion
Asthma mimickers may pose a challenge to clinicians by requiring a more detailed investigation of the presenting symptoms and treatment regimen. They are defined as conditions that could cause episodic obstruction of the airway that results in symptoms similar to asthma. However, they usually do not improve with corticosteroids or bronchodilators. In patients with a known history of asthma, worsening dyspnea, chest tightness, and wheeze usually warrant initial treatment with bronchodilators and corticosteroids. However, if wheeze and dyspnea persist despite receiving adequate treatment, clinicians should have a high index of suspicion for an asthma mimicker, especially if the patient also has atypical symptoms, such as hoarseness, stridor, or chronic cough.

According to a Canadian study, approximately 30% to 35% of adults originally diagnosed with asthma did not have it, which led to inappropriate medication use. Therefore, it is prudent for clinicians to be aware of other causes of dyspnea and wheeze if these symptoms remain persistent despite adequate treatment for them and their exacerbating factors, such as allergies and gastroesophageal reflux (GERD). Asthma mimickers could be divided into extrathoracic and intrathoracic causes (Table 1). However, these categories are indistinct and limit classification in relation to the location in the tracheobronchial tree and lungs, which may exclude some diagnoses such as anxiety and heart failure.

Identification of an asthma mimicker is difficult in a patient who is pregnant. During pregnancy, asthma control may be suboptimal, which contributes to a diagnostic dilemma during an exacerbation because the clinician’s initial inclination pivots around the patient’s history of asthma. Furthermore, exacerbating factors, such as viral infections and GERD, which is usually worse during pregnancy, are related to poorer asthma control. According the Global Initiative for Asthma, approximately one-third of women will experience worsening of their symptoms during pregnancy; one-third of them will experience no difference; and one-third of them will experience improvement. Other considerations surrounding asthma control in pregnancy include treatment challenges. One study found that approximately 65% of women have difficulty managing their asthma during pregnancy, citing issues with inhaler use and understanding which medications to use. Furthermore, pregnant women have a decreased rate of receiving appropriate treatment for asthma exacerbations likely because of concerns for fetal harm. Although the aforementioned reasons could explain poor control of asthma during pregnancy, an asthma mimicker should be considered if asthma treatment is maximized and all of the aforementioned factors are addressed.

Although head and neck cancer would not be the initial consideration in a young, pregnant patient, it should be included in the differential diagnosis in a patient with risk factors, such as cigarette smoking and alcohol use. One of the most common head and neck cancers is laryngeal carcinoma, which accounted for >13,000 new cases in 2016 in the United States. It is especially prevalent in the older population, typically seen in the sixth and seventh decades of life; and it is commonly seen in tobacco users who also consume alcohol, because there is a synergistic relationship. The usual locations for laryngeal carcinoma is in the glottic and supraglottic regions. Across all age groups, well-to-moderately differentiated squamous cell carcinoma is the most prominent histologic finding. Laryngeal carcinoma in younger patients, specifically >40 years old, is rare, with

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the most common causes being human papillomavirus (HPV), GERD, and marijuana use. It has been reported that the amount of HPV infection cases that cause laryngeal carcinoma ranged from 0 to 27%. It is difficult to determine the prevalence of laryngeal carcinoma caused by GERD, especially in the younger population. Even in older patients, confounders such as alcohol and tobacco use make the relationship between GERD and laryngeal carcinoma challenging to substantiate. Based on an epidemiology study, marijuana use was found to be associated with higher rates of p16+ oropharyngeal cancers. A less common cause of laryngeal carcinoma, specifically in women, is endogenous and exogenous hormone exposures, which are thought to be culprits in increasing the risk of head and neck cancers. However, this association has not been established, and there may be an inverse and favorable relationship between endogenous and exogenous hormone exposure and head and neck cancers.

Treatment and prognosis of laryngeal carcinoma vary based on stage of the cancer and age of the patient. Regardless of the age group, intervention should be pursued in a timely manner. One study showed that patients <40 years old were prescribed radiation over surgery, because the likelihood of the development of a second malignancy is low. Additionally, radiation therapy is most pursued in younger populations over laryngectomy with radiation because the combination could lead to poorer quality of life. Older patients who underwent radiation therapy first had a higher rate of surgical intervention. Therefore, surgical intervention is recommended in the older population. One study demonstrated approximately 75% of study participants >40 years old underwent surgery, which included total or partial laryngectomy with cricohyoidopexy; both types of surgical intervention had low rates of eventual need for chemotherapy. In the younger population, prognosis remains contentious because some studies found that this age group was associated with a more aggressive course and poorer outcome; other studies argued that age may play a role in increasing the chance of survival. Although the prognosis remains uncertain, there was no difference in the outcome, given the location of the tumor or staging when patients from the younger or older cohort were compared.

The diagnosis of laryngeal carcinoma in pregnant women is very rare, because cancer in pregnant women generally is uncommon. Treatment options depend on the trimester, with consideration to limit potential harm to the fetus. The best treatment option to ensure the greatest chance of a cure is surgery; however, this ideally should be pursued in the second trimester when the anatomic and physiologic changes are mild, providing a favorable environment for anesthetic techniques that would maximize maternal and fetal safety during surgery. Anesthesiologist would need to account for the adaptive changes of pregnancy and medications that have the potential to be teratogenic to the fetus. If there is a concern for airway compromise and the patient elects to not have a total laryngectomy, a tracheostomy is required. Given the complexity of these cases, these patients require a multidisciplinary approach for treatment.

Clinical Course

The patient had placement of a tracheostomy after biopsy, and her wheeze subsequently resolved. She received a diagnosis of stage II (T3, N1) HPV-mediated squamous cell carcinoma of the larynx. She was hospitalized for 10 days and was seen by the oncology and radiation-oncology staff who recommended...
carboplatin and paclitaxel weekly for a total of seven cycles to initiate 1 week after discharge from the hospital and then radiation therapy after delivery. She started chemotherapy as instructed, and she returned for induction of labor at 34 weeks. She ultimately delivered a healthy baby via cesarean delivery. The PET-CT scan that was obtained after delivery showed a favorable response to chemotherapy with a small amount of residual disease and no evidence of metastasis. After delivery, she started radiation therapy for 7 weeks with favorable response. Repeat PET-CT scans after completion of radiation therapy showed resolution of her glottic tumor and no evidence of metastatic disease.

Clinical Pearls

1. Consideration of other diagnoses is important when evaluating a patient with asthma who presents with dyspnea, wheeze, and hoarseness and not responding to conventional therapies for asthma because the diagnosis could be an asthma mimic, such as GERD, anxiety, and even malignancy.

2. Squamous cell carcinoma of the larynx is rare in younger patients and even more concerning when found in a pregnant woman because the usual treatment modalities have substantial risk for harm to the mother and fetus.

3. In younger populations, HPV is one of the most common causes of laryngeal cancer. Positive p16 staining is a surrogate marker for HPV.

4. Treatment options for pregnant women include tracheostomy, surgical resection with laryngectomy, and fractionated-dose chemotherapy in the second or third trimester. Radiation exposure should be avoided until after delivery.

Acknowledgments

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Suggested Readings


