version of dihydrofolate to tetra-hydrofolate or folic acid, which is a necessary compound for 1-carbon transfer reactions involved in purine synthesis. Trimethoprim competitively inhibits microbial DHFR. The effectiveness of TMP thus depends on the ability of the organism to absorb folic acid from the plasma.

However, failure, to respond to TMP-SMZ occurs in approximately 30 percent of cases of PCP, despite adequate antibiotic serum levels. Initial failure to respond to TMP-SMZ therapy may be reversed by increasing the dose, and this may have been effective in our patient, although retrospectively, drug levels appear adequate by the criteria of Winston et al. However, it would be very unusual for PCP organisms still to be present at day 19 after starting treatment, unless the TMP-SMZ had not been effective. The subsequent dramatic clinical and roentgenographic improvement (Fig 1d) was achieved purely as a response to the withdrawal of folic acid. Physicians should, therefore, be alerted to the possibility that concomitant use of folic acid and TMP-SMZ in the treatment of PCP may result in the failure to effect a cure.

Since this report was written, a further case of relapse of PCP has occurred in this hospital in a renal transplant recipient treated with TMP-SMZ and folic acid; a successful outcome was seen with TMP-SMZ alone.

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Esophageal Cyst as a Cause of Chronic Cough*

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The previously unreported association of chronic persistent cough due to a duplication esophageal cyst is presented. The presence of a long history of atopy, bronchitis, and asthma resulted in a delay in diagnosis. When vigorous bronchodilator therapy was unsuccessful, close observation of the patient and review of her radiographs suggested the esophageal etiology of her cough. This case reinforces the observation that chronic persistent cough, although common, may present a very perplexing problem. A systematic approach considering the anatomy of the cough reflex, and an awareness of the esophageal and other nonpulmonary causes of cough, can aid in diagnosis and management of these patients.

Persistent cough is a common problem which is most often caused by postnasal drip, chronic bronchitis, or asthma. Gastroesophageal reflux may account for 10 percent of the cases despite the absence of classic symptoms. There are numerous reports of other esophageal and nonpulmonary diseases presenting predominantly with persistent cough.

We recently encountered a girl with persistent chronic cough due to an esophageal duplication cyst, a previously unreported occurrence. The presence of a long history of allergic rhinitis, bronchitis, and asthma with objective evidence of hyperreactive airways caused confusion and a delay in diagnosis.

CASE REPORT

A 15-year-old nonsmoking, white girl was referred for evaluation of persistent cough. The patient had a four-year history of bronchitis (one to two episodes per year), allergic rhinitis, "asthma" and an intermittent cough. She had been receiving weekly desensitization shots for two years. Four months prior to admission, she developed an acute episode of cough productive of small amounts of white sputum followed by a persistent residual nonproductive cough. She was evaluated locally with a chest radiograph and pulmonary function testing, both of which were reported as normal. Symptomatic treatment with bronchodilator drugs, narcotic cough suppressants and a short course of prednisone therapy in unknown doses were unsuccessful, and she presented to the authors for evaluation. The patient described her cough as dry, nonproductive, hacking, persistent throughout the day but worse in the recumbent position and just after eating. She complained of frequent palpitations and denied hoarseness, dysphonia, heartburn, hemoptyis, dyspnea on exertion, or weight loss.

Initial physical examination revealed a healthy appearing, 15-year-old white girl with a hacking, paroxysmal, bark-like cough. Blood pressure was 130/60 mm Hg; pulse rate was 120/min, bounding and regular; respirations: 18/min; temperature: 37°C (98.6°F). Head, eye, ear, nose and throat examination was unremarkable, including indirect laryngoscopy and nasopharyngoscopy. Lungs were clear, chest symmetric, and heart without murmur, rub, or gallop. The

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remainder of the physical examination was normal.

While awaiting results of initial laboratory tests and previous radiographs, the patient was closely observed by one of the authors (POK). Her cough was noted to be paroxysmal, persistent throughout the day, nonproductive, and slightly increased in frequency following meals. The cough was dramatically increased in frequency and louder in the recumbent position and persisted while the patient was asleep. Spirometry showed a baseline FEV₁ of 2.7 liters (89 percent of predicted), FVC of 3.14 liters (98 percent of predicted), MMEF of 3.19 L/min (99 percent of predicted). Methacholine inhalation challenge test following a previously described methodology⁴ was positive showing a 26 percent fall in the FEV₁ at 95 cumulative inhalational units with return to baseline after inhaled metaprotenol. Aggressive treatment with theophylline (blood level 18 mg/L), albuterol metered dose inhaler, and 40 mg prednisone daily, failed to decrease either the frequency or intensity of the cough and was discontinued after seven days.

Review of her chest roentgenogram (Fig 1) suggested a 2 × 3 cm mass in the lower third of the esophagus on PA view that was not visible on the lateral view. An upper GI series demonstrated a 4 × 5 cm intraluminal esophageal mass in the distal one third that did not appear to be in continuity with the tracheobronchial tree (Fig 2). There was no hiatal hernia nor evidence of reflux. Gastroesophagoscopy also revealed an intramural mass in the distal esophagus with normal overlying mucosa and no suggestion of esophagitis. The patient was taken to the operating room and underwent fiberoptic bronchoscopy preoperatively. Mild erythema of the distal trachea and carina was noted, but no mass lesion was identified.

Right thoracotomy was performed and a 2 × 3 cm fluid-filled esophageal mass abutting the vagus nerve was identified in the lower third of the esophagus. The mass was freed from the vagus nerve and removed. Pathology was consistent with a duplication esophageal cyst. The patient had an unremarkable postoperative course and repeat barium esophagram one month later showed no residual mass. Eight months following surgery, the patient is totally free of cough and is receiving no antitussive or bronchodilator medications.

DISCUSSION

Much recent attention has focused on the ability of esophageal abnormalities to produce pulmonary symptoms. Recurrent pneumonia, nocturnal aspiration, asthma, nocturnal cough and even progressive pulmonary fibrosis are recognized, but uncommon, presentations of esophageal disease, particularly gastroesophageal reflux. Isolated case reports of Zenker's diverticuli, achalasia and esophageal carcinoma have been implicated as causes of recurrent pulmonary symptoms including chronic cough.⁵ Though the mechanism is not clear, recurrent aspiration in the recumbent position may be responsible for triggering the cough reflex and exacerbating other pulmonary diseases including asthma. Human and dog studies suggest that a vagally mediated reflex may be responsible for asthmatic symptoms associated with reflux disease.⁶ ⁷

Cough receptors are located in the larynx, bronchi and trachea (lower respiratory receptors), as well as the nose, paranasal sinuses, ear canals (Arnold's nerve), pharynx, pleura, pericardium, stomach and the diaphragm. Human and animal studies have demonstrated the afferent impulses to be carried by the vagus (ear canal, stomach, pleura and lower respiratory receptors), trigeminal (nose and sinuses), glossopharyngeal (pharynx), and phrenic (diaphragm, stomach) nerves. The cough center probably resides in the medulla and the efferent pathways are carried via the vagus, the phrenic, and other spinal motor nerves that supply the respiratory muscles. Numerous case reports suggest that a cough can be stimulated anywhere along the afferent pathways; ear wax, nasal polyps, neurilemoma of the vagus nerve, osteophytes of the cervical spine, aneurysms of the

FIGURE 1. PA chest film shows retrocardiac smooth bordered mass on the right side.

FIGURE 2. Detail of barium esophagogram showing compression of the esophagus on the right side with normal-appearing overlying mucosa.
palatine artery, and even a transvenous pacemaker (either through stimulation of pericardial or diaphragmatic receptors) all have been reported as causes of cough.

Because of the myriad etiologies of cough, it is quite possible for any given patient to have more than one possible etiology of their cough. Accordingly, if specific therapy for a given diagnosis fails to relieve the cough, then alternative diagnostic possibilities should be considered. To this end, careful observation of the patient and careful questioning of those living with the patient to define exacerbating or alleviating factors can be very rewarding.

We cannot find another case in the reported literature in which an esophageal cyst produced chronic cough. This patient's esophageal cyst was impinging directly upon the vagus nerve. This close proximity to the afferent cough pathway, the known association of esophageal disease with cough, and the relief she obtained from her cough postoperation argue for a causal relationship between the esophageal cyst and the patient's symptoms.

**Conclusion**

Our patient had a long history of atopy and bronchitis. With this history and the positive result of methacholine challenge we felt that asthma was the most likely etiology of her cough. Failure of vigorous bronchodilator therapy to relieve her symptoms prompted reconsideration of our diagnosis. Careful observation of the patient and review of her data ultimately led to the discovery of the esophageal cyst. The importance of esophageal and other nonpulmonary etiologies of chronic cough must be kept in mind by physicians caring for patients with cough. Failure of specific therapy for any given etiology of cough should lead to a careful reexamination of the patient in an effort to find an alternate cause of the cough. A systematic approach, considering the anatomy of the cough reflex, should lead to a diagnosis and allow specific therapy to be applied.

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