Prolonged Dry Cough without Pulmonary Changes on Radiological Imaging

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Abstract:
A 16-year-old boy who was a non-smoker presented with a prolonged severe dry cough and malaise of 3 months in duration. Despite an increase in the patient’s inflammatory marker levels, no respiratory lesions were radiologically or serologically detected. We suspected that the cough reflex pathway had been stimulated by large vessel vasculitis (LVV, a non-respiratory inflammatory condition) and diagnosed the patient with Takayasu arteritis. While inflammation of either the ascending pharyngeal or pulmonary artery have been reported to cause cough in patients with LVV, the present case shows that intense inflammation of the aortic arch and the starting portion of its main branches may stimulate a vagus nerve branch as a novel mechanism causing cough.

Key words: cough, Takayasu arteritis, large vessel vasculitis

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Introduction
Prolonged cough is the most common symptom encountered in general clinical practice, and vasculitis is a rare cause of cough. The lung is frequently affected in patients with small vessel vasculitis and lung parenchymal lesions induce cough. On the other hand, patients with large vessel vasculitis (LVV), which includes Takayasu arteritis (TA) and giant cell arteritis (GCA), almost never develop lung lesions. However, there are few reports of patients with LVV presenting with prolonged dry cough without pulmonary changes on radiological imaging (1, 2). We herein describe a case of prolonged dry cough in a patient with TA as well as the mechanisms of cough formation.

Case Report
A 16-year-old boy was referred to our department with prolonged severe dry cough and malaise of 3 months in duration. His cough had gradually worsened, causing insomnia. At another hospital, auscultation, plain chest radiography, non-enhanced computed tomography (CT) of the chest and the paranasal sinuses, and testing for allergen-specific immunoglobulin E, Epstein-Barr virus antibody, cytomegalovirus antigen, aspergillus antigen, (1-3)-β-D glucan, and interferon-γ release assay revealed no abnormalities. Treatment with inhaled corticosteroids, a bronchodilator, antiallergic agents, and several types of antibiotics had been ineffective. He had no history of smoking. A physical examination revealed that his blood pressure was 128/76 mmHg with no differences among the four limbs. There was no evidence of angiodynia or bruit. Blood tests revealed increased levels of inflammatory markers.

Although no respiratory lesions were detected either radiologically or serologically, we hypothesized that a hidden non-respiratory inflammatory condition stimulated the cough reflex pathway, causing cough. According to the anatomy of cough reflex pathway, we suspected that the inflammation of the large vessels in contiguity with the pathway, which non-enhanced computed tomography is poor at assessing. Neck and chest helical CT angiography and whole-body contrast-enhanced CT revealed wall thickening of the aortic arch and the starting portion of its main branches (Fig. 1), with no abnormalities in the remainder of the aorta, the main branch arteries, the coronary arteries, the pulmonary arteries, or the...
Figure 1. Coronal chest CT angiography showing wall thickening of the aortic arch (arrows) and the starting portion of its main branches (arrowheads).

Discussion

TA is a chronic inflammatory disease of the large vessels that primarily affects the thoracic aorta and its main branches. Both the pulmonary arteries and the abdominal aorta are also involved in approximately 50% of TA patients (2, 3). Cases of TA are predominantly reported in Asia, especially Japan, but are reported throughout the world. The disease has a female predominance (1:8-9), predominantly occurring in girls and women of 10-40 years of age (3). The clinical manifestations in the early phase include subtle systemic symptoms, such as low-grade fever, weight loss, malaise, and fatigue. An early diagnosis of TA is difficult because the initial symptoms and signs may vary and are generally nonspecific. As the disease progresses, varied ischemic or neurologic symptoms, such as headache, syncope, stroke, and arm claudication may manifest according to the area of vascular involvement (Table). Myalgia and arthralgia are occasionally observed; arthritis is a rare manifestation (4). Skin lesions and gangrene have rarely been reported (5). Although the pulmonary arteries are involved in approximately 50% of all cases of TA (2), cough is a rare symptom (3, 6). Radiologically, both CT angiography and magnetic resonance imaging clearly depict various luminal and mural changes in the aorta and its major branches while neither non-enhanced CT nor angiography is suitable for assessing arterial wall thickening. In this case, a 16-year-old boy with TA presented with a 3-month history of severe dry cough and malaise. It is difficult to suspect TA based on the clinical presentation because the cardinal symptom was prolonged severe cough and there were no ischemic or neurologic symptoms suggesting TA. Cough is observed as a chief complaint at the onset of TA, in 1.5% of patients (3). While non-enhanced chest CT revealed normal findings, CT angiography successfully depicted wall thickening of the aortic arch and the starting portion of its main branches with no abnormalities in the remainder of the aorta, the main branch arteries, the coronary arteries, or the pulmonary arteries, which corresponds to the angiographic classification of type IIa, which accounts for 16.3% of patients with TA (3).

Cough is the most common symptom that physicians encounter in general clinical practice. It is a defensive reflex that excretes excessive secretions and particulate matter, and protects against the aspiration of foreign materials. Impulses from stimulated cough receptors traverse an afferent pathway via the vagus nerve to the cough center in the medulla. The cough center generates an efferent signal that travels down the vagus, phrenic, and spinal motor nerves to the expiratory muscles, resulting in coughing. Inflammatory or mechanical changes as well as chemical or mechanical irritants trigger airway cough receptors and innervate the vagus nerve, especially in the larynx, the carina, and other points where the proximal Airways branch (Fig. 2). In addition, branches of the vagus nerve are located in the external auditory canals, eardrums, paranasal sinuses, diaphragm, distal esophagus, pleura, pericardium, and stomach, and the stimulation of these areas can evoke a cough reflex (Fig. 2).

There are few reports of patients with LVV presenting with prolonged dry cough without pulmonary changes on radiological imaging (1, 2). The large vessels in the cervicothoracic area include the internal carotid, external carotid, and pulmonary arteries in addition to the aorta and its main branches, which adjoin the vagus nerve branches and plexuses, as well as cough receptor-rich areas of the respiratory tract. Although the mechanisms of cough formation in LVV are not completely clear, it appears that LVV stimulates the neighboring cough receptors or the vagus nerve, and produces a cough through the above cough reflex route. In our opinion, based on the thickness of the airways, the stimulation of the vagus nerve is a more likely cause of cough than the cough receptors in the airway lumen. TA and GCA share the affected arteries and the mechanisms of cough formation overlap. The following concepts were introduced to explain the area involved by LVV that causes cough. First, inflammation of the pulmonary arteries, the proximal areas of which adjoin the pulmonary plexuses of the vagus nerve, appears to cause cough (2). They are involved in approximately 50% of all cases of TA but are rarely involved in GCA. Second, it is assumed that inflammation of the ascending pharyngeal artery, a branch of the external carotid
The ascending aorta Dyspnea due to aortic regurgitation
Increased pulse pressure and pndiastolic murmur

The subclavian artery Arm claudication
Blood pressure difference between arms and reduced peripheral arterial pulse

The vertebral artery Vertigo or syncope due to arm exercise (subclavian steal syndrome), convulsion, and stroke
Orthostatic syncope

The carotid artery Headache, convulsion, stroke, jaw claudication, and visual impairment
Carotidynia, carotid bruit, and orthostatic syncope

The coronary artery Angina pectoris and myocardial infarction
Carotidynia, carotid bruit, and orthostatic syncope

The pulmonary artery Chest pain, dyspnea, hemoptysis, cough, pulmonary hypertension, and pulmonary thrombosis
Abdominal aorta tenderness

The abdominal aorta Abdominal pain and back pain
Abdominal aorta tenderness

The mesenteric artery Abdominal pain, diarrhea, and gastrointestinal hemorrhage
Abdominal aorta tenderness

The renal artery Renovascular hypertension and ischemic nephropathy
Abdominal bruiz

Figure 2. Branches of the vagus nerve located along the large vessels.

artery, which adjoins the pharyngeal branch of the vagus nerve, is a cause of cough (7). The abdominal aortitis, which adjoins the esophageal plexus of the vagus nerve, may also cause cough. In this case, neck and chest CT angiography did not detect vasculitis in either the pulmonary or the ascending pharyngeal artery. There was no sign of abdominal aortitis on contrast-enhanced CT. Although further studies are needed, on the basis of the angiographic findings and its very high sensitivity (95%) (8), the intense inflammation of the aortic arch and the starting portion of its main branches may stimulate a vagus nerve branch as another novel mechanism of cough formation.

We herein presented a case in which prolonged dry cough was a rare manifestation of TA and our hypothesis regarding the mechanism of cough formation. The diagnosis of TA is often delayed because the initial symptoms, signs, and laboratory findings may vary and are generally nonspecific. The selection of an appropriate imaging procedure is necessary to make a diagnosis of TA, which is a rare cause of prolonged cough. This may negate the need for expensive cross-sectional laboratory and imaging tests, and avoid unnecessary treatment delays.

Written consent to publish this case report was obtained from the patient and the patient’s guardian.

The authors state that they have no Conflict of Interest (COI).

References

1. Zenone T, Puget M. Dry cough is a frequent manifestation of giant cell arteritis. Rheumatol Int 33: 2165-2168, 2013.
2. Manganelli P, Fietta P, Carotti M, Pesci A, Salaffi F. Respiratory system involvement in systemic vasculitides. Clin Exp Rheumatol 24: S48-S59, 2006.

3. Watanabe Y, Miyata T, Tanemoto K. Current clinical features of new patients with Takayasu arteritis observed from cross-country research in Japan: age and sex specificity. Circulation 132: 1701-1709, 2015.

4. Karageorgaki ZT, Bertsias GK, Mavragani CP, et al. Takayasu arteritis: epidemiological, clinical, and immunogenetic features in Greece. Clin Exp Rheumatol 27: S33-S39, 2009.

5. Rocha LK, Romitti R, Shinjo S, Neto ML, Carvalho J, Criado PR. Cutaneous manifestations and comorbidities in 60 cases of Takayasu arteritis. J Rheumatol 40: 734-738, 2013.

6. Lupi E, Sanchez G, Horwitz S, Gutierrez E. Pulmonary artery involvement in Takayasu’s arteritis. Chest 67: 69-74, 1975.

7. Larson TS, Hall S, Hepper NG, Hunder GG. Respiratory tract symptoms as a clue to giant cell arteritis. Ann Intern Med 101: 594-597, 1984.

8. Yamada I, Nakagawa T, Himeno Y, Numano F, Shibuya H. Takayasu arteritis: evaluation of the thoracic aorta with CT angiography. Radiology 209: 103-109, 1998.

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