Editor's key points

- In patients presenting with a chronic cough, maintain a broad differential diagnosis including asthma, chronic obstructive pulmonary disease, gastroesophageal reflux disease, and drug side effects.
- Chronic cough is a rare but possible side effect of statin use.
- Discontinuing or rotating statins are both reasonable options to confirm the role of statins in a chronic cough.

Points de repère du rédacteur

- Chez les patients qui présentent une toux chronique, on doit envisager un large éventail de diagnostics différentiels, notamment l'asthme, la maladie pulmonaire obstructive chronique, le reflux gastro-œsophagien pathologique et les effets secondaires de médicaments.
- La toux chronique est un effet secondaire rare, mais possible, de l'utilisation de statines.
- La cessation ou la rotation des statines sont toutes deux des options raisonnables pour confirmer le rôle des statines dans la toux chronique.

Chronic cough associated with statin use in a 74-year-old man

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Chronic cough is a common concern in primary care, with an estimated prevalence of 16% in Canada.[1] Guidelines recommend deprescribing medications such as sitagliptin and angiotensin-converting enzyme inhibitors in patients with chronic cough, as it may be a side effect of these medications.[2] Nearly 50% of Canadians 40 years or older have a diagnosis of dyslipidemia or are being treated with a lipid-lowering agent.[3] However, family physicians may be unaware that statins can cause chronic cough as a side effect.

Case

A 74-year-old man with a remote history of a myocardial infarction presented to his family physician for routine chronic disease management. He complained of a dry cough that began approximately 15 years prior. The cough was not progressing and not associated with hemoptysis, weight loss, fever, chills, or chest pain. He complained of exertional dyspnea and fatigue in the past few years that he thought was due to physical deconditioning. He denied any typical heartburn symptoms and was not known to have any chronic lung disease or malignancy. He denied any nasal congestion or rhinorrhea.

The patient worked in a wire factory for 44 years. He was knowingly exposed to asbestos for about 20 of those years. He did not use any form of respiratory protection during his employment. He did not have any other known inhalant exposures such as bats, grain, or mould. He smoked cigarettes but quit more than 30 years prior to presentation. He had no family or personal history of chronic lung disease or lung cancer.

His past medical history included hypertension, hyperlipidemia, and ischemic heart disease, for which he was taking 40 mg of oral telmisartan once daily, 40 mg of oral atorvastatin at bedtime, and 81 mg of oral acetylsalicylic acid once daily, respectively. His other medications were vitamin D3, cholestyramine, and pantoprazole.

The patient believed his cough began when he started taking atorvastatin after his myocardial infarction, though he was prescribed telmisartan at that time. He found the cough improved if he stopped taking the atorvastatin for a few days.

On examination, he looked well. His vital signs, including respiratory rate and pulse oximetry, were normal. His cardiovascular and respiratory examination findings were unremarkable.

Investigation

Given the patient's history of asbestos exposure, we performed computed tomography (CT) scans of the chest. There were shallow noncalcified pleural plaques bilaterally, suggesting mild changes of asbestos-related pleural disease. A minor degree of subpleural reticulation at bilateral lower lung zones without honeycombing fibrosis was seen, which may have reflected some minimal or early fibrosis changes. Evidence of remote previous granulomatous infection with tiny punctate granulomas was seen in the left lung, as was a small calcified right hilar lymph node.

Differential diagnosis

Common causes of chronic cough include asthma, gastroesophageal reflux disease, upper airway cough syndrome, or nonasthmatic eosinophilic bronchitis.

The patient's CT findings were suggestive of mild asbestos-related pulmonary disease, but he declined a referral for biopsy to definitively rule out mesothelioma. Pulmonary function testing was not available to rule out asthma or chronic obstructive pulmonary disease (given his occupational exposures). The patient's blood eosinophil count was normal. He was known to have gastroesophageal reflux disease but his symptoms were well controlled with pantoprazole therapy. Given the history of improvement of his symptoms with discontinuation of atorvastatin, the patient was switched from 40 mg of atorvastatin to 20 mg of rosuvastatin orally at bedtime. The patient's cough resolved a few weeks after switching to rosuvastatin.

Discussion

3-Hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, commonly known as statins, are fundamental in the management of cardiovascular disease. Statins reduce cholesterol biosynthesis by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A reductase, which increases expression of low-density lipoprotein receptors in the liver and enhances hepatic clearance of low-density lipoprotein.[4] Statins have anti-inflammatory effects, leading to their use in primary and secondary prevention of cardiovascular disease.[4] Adverse events owing to statin use include hepatotoxicity and myopathy, as well as interactions with other medications.[4]

Respiratory adverse events (RAEs) associated with statin use have been documented, ranging from dry mouth and chronic cough to interstitial lung disease (ILD) and restrictive lung disease.[5-7] The exact mechanism by which statins cause RAEs remains unknown but some researchers postulate that increased activity of prostacyclin and nitric oxide after the administration of statins may play a role,[8,9] as prostacyclin and nitric oxide increase the sensitivity of the cough reflex in humans and guinea pigs.[10,11] There are few studies reporting or investigating the relationship between statins and cough and most are case studies. The prevalence of statin-related ILD is estimated to be 0.01% to 0.4%; only a small fraction of patients who reported statin-related cough also had documented lung injury.[8,12] The prevalence of other statin-induced cough remains unknown but is likely higher based on observational studies.[5]

The patient in this case had chest CT findings suggesting mild asbestos-related disease, which was supported by his occupational exposure history. Although fibrosis may be seen in cases of statin-induced ILD, the most common finding is ground-glass opacities, which were absent in this patient.[6]

The key finding in this case was complete symptomatic resolution after discontinuing atorvastatin. Using the Liverpool Causality Assessment Tool,[13] the likelihood of atorvastatin causing the cough in this case is probable. Previous studies have suggested that statin-induced cough may be a class effect but there is inconclusive evidence of increased likelihood of cough with 1 statin versus another.[7,8] Carnovale et al analyzed spontaneous reports of statin-induced cough between 2004 and 2012,[8] with rosuvastatin first being marketed in the United States in 2003.[14] There may have been disproportionately higher reports of adverse drug events with rosuvastatin compared with other statins due to the Weber effect, where spontaneous reporting of adverse drug events is highest in the first years after the drug is initially approved.[15]

Conclusion

Statin-induced RAEs are uncommon but should be considered in the differential diagnosis for a patient presenting with respiratory symptoms after starting a statin. Given the resolution of symptoms after switching to rosuvastatin in this case, it is reasonable to trial a different statin in patients who develop RAEs. As the risk of RAEs is far lower than the benefit of secondary prevention, prescribing practices related to statins should not change. Future studies should investigate the mechanisms by which statins result in RAEs, the prevalence of statin-induced cough without ILD, and if individual statins result in fewer RAEs.

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Competing interests
None declared

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