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Case report

Longstanding tracheobronchomalacia: A forgotten cause of severe cough and its response to roflumilast

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ABSTRACT

This case report describes a patient with moderately severe tracheobronchomalacia following mycoplasma pneumonia. The patient was considered to have obstructive lung disease despite no prior smoking or lung disease and failure to respond to standard treatment. The possibility of tracheal pathology causing cough and sputum was not considered in 23yrs confirming this to be a "forgotten zone". The patient was treated with Roflumilast to reduce airway secretions with great success and the Immunology of Roflumilast is discussed.

1. Case history

A 73yr old man was referred for a further opinion on his 23 year problem of persistent cough with difficulty expectorating. The onset appeared to follow a mycoplasma pneumonia associated with a pericarditis, prior to which he had no respiratory diseases at all. He had never smoked and previous CT scans of his chest and sinuses were report normal without evidence of sinus disease, bronchiectasis or chronic obstructive pulmonary disease to account for his persistent cough and sputum. When expectorated his sputum was opalescent mucoid material and yellow or green during infections. In the 23yrs of this affliction the working diagnosis had mainly been COPD as past spirometry was always reduced: PEFR 70% predicted, FEV1 81% predicted, FVC 68% predicted.

He had worked in the building trade and his BMI was 34. Treatment for COPD and asthma in the form of long acting anti-muscarinics and long acting beta-2 agonists with inhaled steroids gave no benefit and he felt made things worse. Assessment of the immune system excluded immunodeficiency and allergy. Regular physiotherapy, an acapello device and carbocisteine failed to shift sputum or improve symptoms. Exacerbations due to a viral illness on top of this chronic cough and sputum occurred up to 4-times a year, when wheeze could be heard requiring steroids with antibiotics to settle him back to his usual baseline.

Sleep was also disturbed by the need to cough, resulting in fatigue and chest pains from incessant efforts to clear sputum. Cardiac investigations were normal. Enalapril for hypertension had been discontinued without benefit to his cough many years before. There was no history of choking on food or drink and nothing to suggest aspiration or micro-aspiration, and his voice was normal.

His past medical history included hypertension, type-2 diabetes mellitus, a hiatus hernia and diverticular disease. Medication consisted of bisoprolol 2.5mg, Ezetimibe 10mg, felodipine 2.5mg, Irbesartan 300mg, liraglitide 1.2mg daily subcutaneously, metformin 1.5 gms/day, Vitamin D3 1000units/day, co-codamol 8hrly as required.

Azithromycin 250mg on Monday and Friday had given benefit to the cough and reduced sputum volume for up to 18 months following which he relapsed back to his prior state despite continuing that treatment. As every avenue had now failed to benefit him, he was left to manage as best he could. In November 2018, due to his poor life quality from his chronic cough, he was referred for further opinion. He gave a very clear account of all that had gone before. On auscultation he had audible loose sputum rattling over his large airways that did not clear with coughing and without associated wheeze. Expectorating the material was difficult and made no discernible difference to the cough, as any successful clearance still left more sputum waiting to be cleared. Spirometry then showed Fev1 2.2L (predicted 81%), FVC 2.6 (74%), PEFR 350 (predicted 72%).

Bronchoscopy (his first) was performed which showed normal nares, no sinus discharge but glue-like secretions clinging to the laryngeal wall with acid burns to the vocal cords. The cords were normal and adducted fully, indicating that cough should be effective. The trachea was tortuous with a reduction in the tracheal lumen longitudinally upon

Abbreviations: COPD, chronic obstructive airways disease; FEV1, forced expiratory volume in 1 second; PEFR, peak expiratory flow rate; TM, Tracheomalacia; TBM, tracheobronchomalacia; EDAC, excessive dynamic airway collapse; CT, computerised tomography; EGFR, Epithelial growth factor receptor.

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coughing from bulging-in of the posterior membrane of the trachea (excessive dynamic airway collapse). The carina was significantly reduced to <5mm in its AP diameter on expiration suggesting tracheobronchomalacia, and closed completely upon coughing trapping secretions below the carina. There were copious glue-like secretions in both main bronchi undoubtedly from failure to be expectorated into the trachea but the distal airways were otherwise normal. These secretions were irritating the airway and triggering the cough receptors. Bacterial and TB cultures from bronchial washings were negative but the secretions showed a neutrophil infiltrate.

A niopam swallow test was normal without aspiration onto the trachea. No hiatus hernia was present but occasional tertiary contractions were noted.

In view of the known immunological effects of roflumilast on bronchial secretions, a trial of this drug at the regular dose of 500mcg/day was commenced. After 1 month there was a possible reduction in cough. As sputum in the airway reduced, his need to cough reduced with an improved quality of life and better sleep.

Symptoms have improved by the month since commencing roflumilast. A dynamic CT scan of the trachea and carina confirmed expiratory airway collapse that was more marked on the left (see Fig. 1) and consistent with tracheobronchomalacia. This condition can be treated with airway stenting; but stents themselves can move and may cause infection and coughing. This is the first report of roflumilast treatment used to reduce airway secretions and cough in tracheobronchomalacia.

His sleep is now prolonged without disturbance by cough and daytime coughing is greatly reduced giving a significant improvement in life quality (score 8 out of 10 for improvement) relative to what had gone before. Spirometry in December 2019; Fev1 2.1 (predicted 77%) FVC 2.62 (predicted 72%), PEFR 340 (predicted 75%). There have been no exacerbations, emergency hospital attendances nor steroid or antibiotic required in the 18 months on treatment.

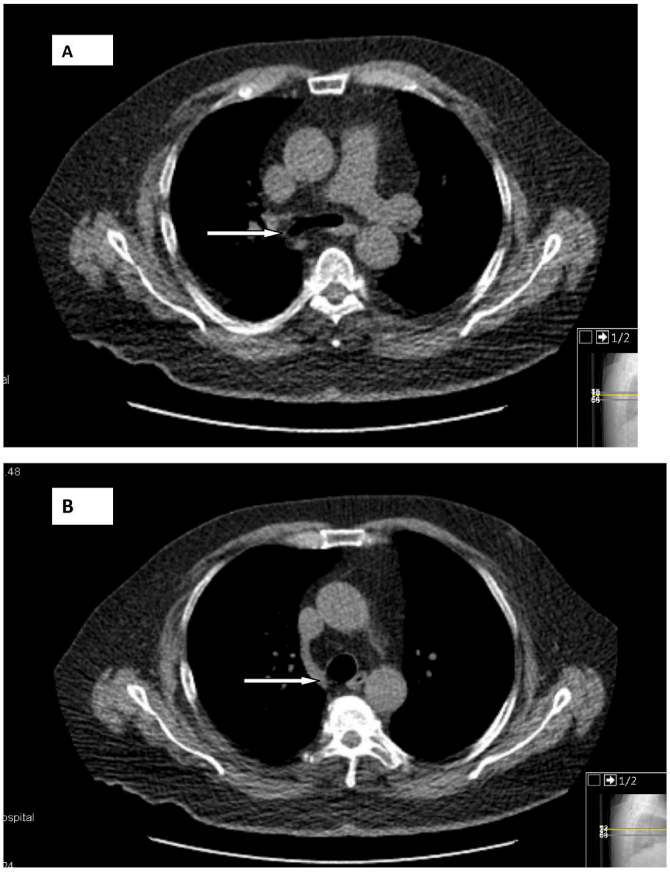

Fig. 1. Show tracheal narrowing in expiration (**A**) and trachea in inspiration (**B**) with dynamic CT views taken just above the carina.

2. Tracheobronchomalacia

The trachea has the potential to be the forgotten zone and doesn't receive much prominence or clinical consideration in the differential diagnosis of chronic cough with sputum [1].

The upper airway includes all the structures from the nasopharynx down to the carina. The trachea is beyond visualisation except by Bronchoscopy or CT scan. It can be affected by infectious or systemic inflammatory diseases, trauma, congenital abnormalities and even malignancy. External compression by adjacent structures can also occur [2] (See Table 1). Patients with tracheal abnormalities are frequently misdiagnosed as having obstructive lung disease but do not respond to bronchodilators which can worsen the condition by relaxing smooth muscle.

[3]. The normal trachea is slightly oval in shape with an AP diameter that is greater than its transverse diameter and resists deformation during a normal and a forced respiratory cycle (Fig. 1).

Tracheomalacia (TM) causes dynamic collapse of the trachea in expiration. This occurs through loss of tracheal rigidity or loss of cartilage integrity with susceptibility to collapse that can be localised or diffuse [4]. This can produce symptoms of chronic cough with sputum and occasionally haemoptysis. TM may impair clearance of secretions and give increased risk of respiratory infection. Most cases are simply considered to have respiratory infections due to a lack of clinical awareness of this condition. Occasionally it is an incidental finding during other investigations with its significance not fully recognised. In TM, the AP diameter of the trachea is reduced to give a crescent shape deformity also known as a scabbard shape.

If only the lateral walls of the trachea narrow, this is a called a sabre-sheath type deformity which is rarer but associated with COPD resulting from mechanical forces of hyperinflation and hyper compliance distorting the intrathoracic trachea.

Clinically relevant TM requires >70% narrowing of the trachea in expiration relative to inspiration to confirm the diagnosis. Some cases may therefore be missed if narrowing is in the 50–70% range. TM is considered mild if the trachea AP-diameter is reduced to <50% in expiration, moderate if reduced by >70% and severe if the walls touch. Tracheobronchomalacia (TBM) is the term used to describe the condition when the main stem bronchi are also involved in expiratory collapse as well as the trachea as in this patient's case [2,5].

Experiments show the FEV-1 still remains >90% of predicted until the tracheal orifice is reduced to 6mm. Spirometry is therefore not a sensitive measure of TM or TBM. In such cases reduced spirometry is attributed to asthma or COPD. Peak flow abnormalities are more sensitive. Flow/volume loops can be abnormal (a saw-toothed pattern in the expiratory flow) and give clues to airway collapse but only when the upper airway narrows to <8mm, so they do not preclude an upper airway disorder from the differential diagnosis. When there is dyspnoea at rest the trachea is reduced to 5mm!

Excessive dynamic airway collapse (EDAC) occurs due to weakness

Table 1
Causes of tracheomalacia.

Infections	**Viral (H1N1, adenovirus, corona virus), bacterial, fungal (aspergillosis).**
Inflammatory/ infiltrative	Sarcoidosis, amyloidosis, rheumatoid, Wegener's granulomatosis, mustard gas, necrotising tracheitis, polyangiitis
Non-inflammatory	Trauma, idiopathic tracheal stenosis, Mounier -Kuln syndrome. Relapsing polychondritis.
Iatrogenic	Post tracheal intubation, high dose prednisolone
Neoplastic	Primary or secondary
Extrinsic compression	Lymph node enlargement, vascular anomalies, fibrosing mediastinitis, mediastinal granuloma, goitre

and bowing of the posterior tracheal membrane into the trachea giving an inverted U-shaped airway with >50% reductions in sagittal diameter during expiration. Unlike TM or TBM, EDAC is not related to structural or functional cartilaginous pathology but may coexist [1,6].

Examination of the trachea should be considered in patients with atypical features or those in whom treatment failure occurs or appears to run a difficult clinical course. To make a diagnosis at Bronchoscopy, narrowing of the tracheal AP diameter should be >70% when directly viewed under tidal breathing and also forced expiratory manoeuvres. This is a gold standard method for evaluating airway collapse.

Dynamic expiratory CT imaging of the trachea has emerged as a non-invasive alternative to Bronchoscopy and can be very useful for large airway pathology. Dynamic CT in TM shows comparable accuracy to Bronchoscopy with greater end expiratory sensitivity [7].

Acquired TM in adults is commonest in men >40yrs and recognised causes are listed in Table 1.

2.1. Immunology of roflumilast

Roflumilast is a selective phosphodiesterase-4 inhibitor now licensed for severe Chronic Obstructive Pulmonary Disease (COPD) with frequent exacerbations. There is particular benefit for those with a significant daily component of chronic bronchitis [8]. Roflumilast gives increased levels of intracellular cyclic AMP which produces a wide range of anti-inflammatory effects. This includes reduced inflammatory mediators and cell surface markers with reduced apoptosis. It is clear from animal studies that roflumilast affects different parts of the immune system changing mediator release relevant to airway remodelling in both COPD and chronic asthma through its effects on cellular cyclic AMP [9].

Roflumilast selectively reduces pro-inflammatory cytokines and growth factors believed to be involved in the pathogenesis of airway disease in asthma (Table 2). In murine models of chronic asthma, roflumilast reduces airway inflammation and hyper-responsiveness with reduced goblet cell hyperplasia and fibrosis, that are involved in airway remodelling and the proliferation of fibroblasts [10].

In COPD, roflumilast significantly reduces sputum neutrophilia and eosinophilia by 35% and 50% respectively relative to placebo treatment. These reductions in sputum cell counts are proportional to the cells already in the sputum and include monocytes and lymphocytes. As a result, the release of neutrophil and eosinophil inflammatory signals are reduced (Table 2). There is a reduction in the sputum concentrations of alpha-2 macroglobulin indicating reduced micro-vascular leak which may be the mechanism of the reduced sputum cell counts [9]. In COPD, spirometry improves with roflumilast treatment relative to placebo along with significantly reduced exacerbations [8].

Table 2
Immunological effects of Roflumilast.

Mediator	Action of mediator	Effect of roflumilast	reference
Interleukin-6	Activates monocytes, fibroblasts and B cell.	↓	15–17
Interleukin-8	Enhances neutrophil chemotaxis	↓	15–17
Tumour Necrosis factor α	From leucocytes and activates inflammatory cells + increases e-selectin on vascular endothelium	↓↓	15
E-Selectin	Increases movement of leucocytes into endothelium	↓	18
Transforming factor β1	Cell growth + proliferation + apoptosis	↓	15
Eosinophil cationic protein	Cytotoxic + promotes fibrosis	↓	9
Neutrophil elastase	Stimulates mucus secretion + degrades connective tissue	↓↓	19
Fibroblast growth factor	Regulates cell proliferation + wound repair	↓	15

In the respiratory tract, mucus is a critical component of innate host defence; in the bronchial airways this is produced by goblet cells and sub-mucous glands. Mucus hyper-secretion is a hallmark of chronic airways disease with animal models identifying activation of epithelial growth factor receptor (EGFR) as central to this. EGFR expression is increased by TNF-α (tumour necrosis factor-α) and positively correlates with the level of goblet cell hyperplasia. Both neutrophils and monocytes can generate TNF-α along with reactive oxygen series and both can activate EGFR. It is likely that the reduction in airway neutrophils and also the ability of roflumilast to reduce TNF-α has reduced mucus production in this patient probably via effects upon EGFR expression [11,12].

Roflumilast is well tolerated with a bioavailability of 80%. The parent drug is 3-times more potent than its metabolite. Metabolism is hepatic via the cytochrome P450 system (phase 1) followed by conjugation (Phase 2). Hepatic dysfunction may impair elimination but a dose adjustment is not required, although severe hepatic dysfunction is a contraindication to use [13].

The co-prescription of drugs that are strong cyp3A4 or dual cyp 3A4 + cyp 1A2 inhibitors such as erythromycin, ketoconazole, fluvoxamine, enoxacin, cimetidine, and rifampicin should be avoided. Azithromycin has only weak effects on cyp3A4 without producing adverse effects if taken with roflumilast. Patients taking glucagon-like peptide-1 (incretin) to stimulate insulin release from the pancreas in diabetes may have increased drug levels with improved glycaemic control. The manufacturers suggest avoiding concomitant theophylline.

Side effects from roflumilast include nausea, diarrhoea and weight loss, insomnia and reduced appetite. They should be avoided in patients with prior immune suppression in case of detrimental effects [14].

3. Conclusion

The ability of roflumilast to reduce airway secretions in chronic bronchitis along with its other known immunological properties as a selective phosphodiesterase-4 inhibitor was the reason why it was considered for this patient. Benefit to the patient has been life transforming without any significant side effects, improving with treatment duration and no exacerbations have occurred on treatment. Lung function shows a small improvement, but the main benefit is through reduced airway secretions with reduced cough. Roflumilast may have benefits in other respiratory diseases though its immunological effects including of course asthma and possibly hypersensitivity pneumonitis and even Sarcoidosis.

This case report describes a patient with moderately severe tracheobronchomalacia following mycoplasma pneumonia. The patient was considered to have obstructive lung disease despite no previous smoking or lung disease and clear failure to respond to standard treatment. The possibility of tracheal pathology causing cough and sputum was not considered in 23yrs confirming this to be a forgotten zone.

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Declaration of competing interest

The authors have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmcr.2020.101247.

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