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Chronic Respiratory Tract Infection by *Escherichia coli* causing Cavitating Lung Lesions

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Abstract

In July of 2020, a 79-year-old woman with a background of bronchiectasis was referred to the Mackay Base Hospital respiratory department for assessment of her productive cough that had progressively worsened over six months. Radiological evaluation of the thorax revealed diffuse thick-walled cavitating lesions bilaterally, greater than 4mm in size, and surrounded by homogenous consolidation. Following extensive investigations with no conclusive diagnosis, our patient underwent a bronchoscopy. Samples from the patient's bronchial wall and lingula were obtained via bronchoalveolar lavage and revealed growth of gram-negative anaerobic *Escherichia coli* (*E. coli)* – a facultative bacterium more commonly found manifesting the gastrointestinal and urological tracts. In this article, we report a rare case of *E. Coli* colonising the respiratory tract with diffuse thick-walled cavities despite antibiotic therapy.

Keywords: *Escherichia coli*; Cavitating lung lesion; Gram-negative cavitation; Thick-walled cavitating lesions

Introduction

A wide variety of diseases manifest as cavitating lung lesions, including pathological processes unrelated to the respiratory system. The cause of cavitation can be classified as infectious and non-infectious. Infectious pathogens include bacteria (ie. *Klebsiella pneumoniae*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Nocardia*, and *Burkholderia Pseudomallei)*; tubercular and non-tubercular mycobacterium; endemic fungi (*cryptococcus*); and parasites. Non-infectious processes include malignancy, vasculitis, and rheumatological origins [1,2].

E. coli is a gram-negative bacillus that forms part of the normal commensal intestinal flora. The strain that inherently inhabits the gastrointestinal system lacks virulence here. Infection occurs when *E.coli* translocates to extraintestinal locations via aspiration or hematogenous dissemination; or when pathogenic strains (ie.ETEC and EHEC/STEC) are ingested; or through environmental transmission in health-care settings [3]. Despite it being a major cause of urinary, intestinal and perineal infections, *E. coli* rarely colonises the respiratory tract and only a few cases have been previously reported [4,5].

Case Presentation

The patient was a 79-year-old female with a background of bronchiectasis who had been seen previously in our respiratory clinic for surveillance of a lung nodule in the right upper lobe. She was discharged from the clinic in 2015 following two years of stable radiological findings. In 2020 the patient was referred to the clinic again for increased cough and sputum production over six months. She denied dyspnoea, haemoptysis, chest pain, or constitutional symptoms. She was a former smoker with a 45-pack-year history and had no environmental or tuberculosis exposures. Her medical history consisted of bronchiectasis of the right middle lobe and chronic kidney disease secondary to hypertension. Of particular importance, her general practitioner reported that she had a urinary tract infection in 2018 with physical signs of systemic involvement and a urine culture positive for *E. coli.* Her medications included telmisartan, prolia injections, and panadol osteo. Physical examination revealed a frail and underweight (39kg) woman who was mildly tachypnoeic at 22 breaths per minute. She was talking in full sentences with no accessory muscle use and maintaining oxygen saturations of 98%

on room air. Auscultation of her heart and lungs was unremarkable.

Formal lung functions testing revealed an obstructive picture (FEV1/FVC ratio of 63.31%) with evidence of small airway disease (MFEF 39%), gas trapping (RV 132.9%), and impaired volume corrected gas diffusion (KCO 72.6%) consistent with her background of bronchiectasis.

Chest imaging in April 2013 using high-resolution computed tomography (HRCT) revealed multiple centrilobular nodules with a spiculated lesion in the right upper lobe, along with bronchiectatic changes and tree in bud inflammation. The spiculated right upper lobe lesion was monitored over a 2-year period. In April 2013 (Figure 1) it measured 10 x 7mm and in October 2014 (Figure 2) the size remained unchanged. Consequently, our patient was discharged from the clinic. She was referred again in July 2020 due to worsening respiratory symptoms. Imaging of the thorax at that time revealed a cavitating lesion in the right upper lobe measuring 1.8 x 1.4cm (Figure 3). This was the previously solid nodule that had remained stable over two years of interval CT scanning.

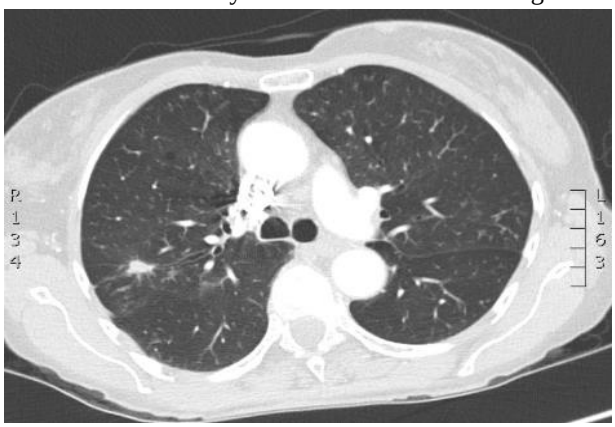

Figure 1: *HRCT chest axial (April 2013) showing original nodular density in right upper lobe inferiorly. Measuring 10 x 7mm.*

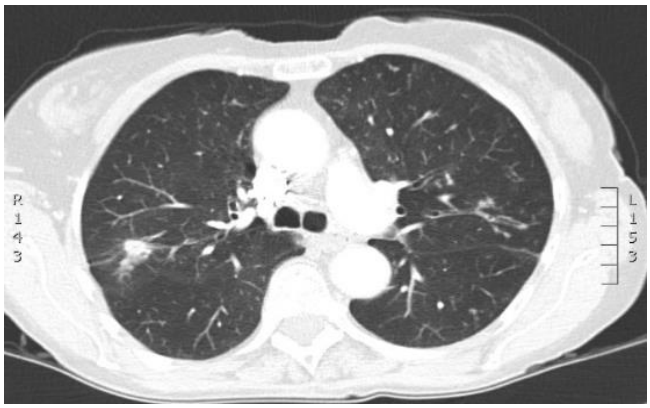

Figure 2: *HRCT chest axial (October 2014) showing RUL lesion measuring 10mm in maximal diameter. Stable interval changes for 2 years and patient discharged from clinic.*

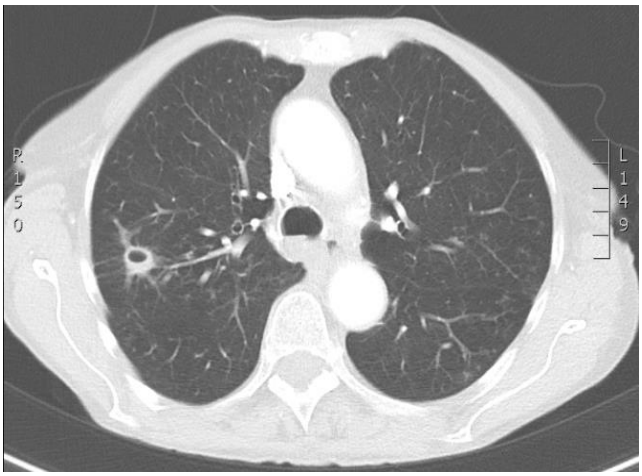

Figure 3: *HRCT chest axial (July 2020) showing progression of RUL nodule to thick-walled cavitating lesion with margins of 18 x 14mm.*

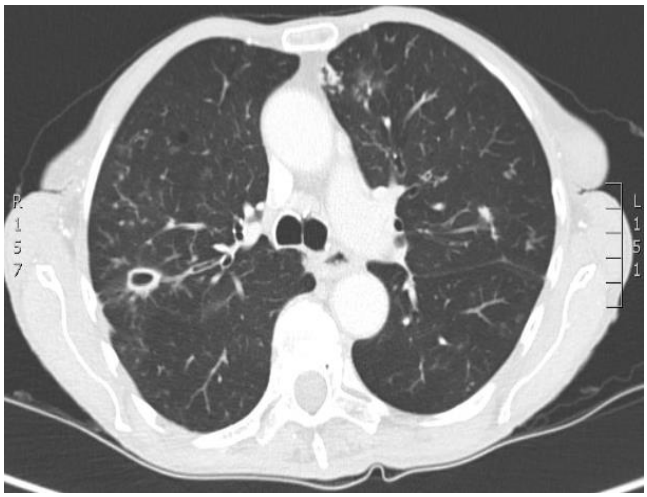

Figure 4: *HRCT chest axial (February 2021) with further growth of lesion – 18 x 8.1mm – despite antibiotic therapy.*

The patient was commenced on antimicrobial therapy sensitive to *E. Coli* in December 2020. A repeat CT scan of the chest two months later (February 2021) showed progressive growth of the lesion despite antibiotic therapy – measuring 18 x 8.1mm (Figure 4). We reference the cavitating lesion in the right upper lobe since it was the first lesion detected on imaging in April 2013 as well as being the largest in size. However, consistent imaging showed the emergence of multiple other cavitating lesions scattered bilaterally, as shown in (Figures 5 and 6).

Bronchoalveolar washings (collected in November 2020) from the left main bronchi, left lower lobe, right middle lobe and right upper lobe all revealed growth of *E. coli.* The washings yielded cloudy mucoid fluid that was moderately blood-stained. All the *E. coli* isolates were resistant to ampicillin, gentamycin, and tobramycin, with sensitivity to amoxycillin/clavulanic acid, cefazolin, trimethoprim/sulfamethoxazole, and meropenem. Mycobacterial cultures, malignant cells, and viral respiratory

panels returned negative. There was no evidence of bacteraemia in blood and her QuantiFERON-TB Gold was negative. A urine culture was not performed. Full blood count showed a leucocytosis with elevated neutrophils, eosinophils, and monocytes. Following consultation with the infectious disease specialist it was recommended that we also obtain serology for melioidosis and cryptococcal antigen, both of which returned negative.

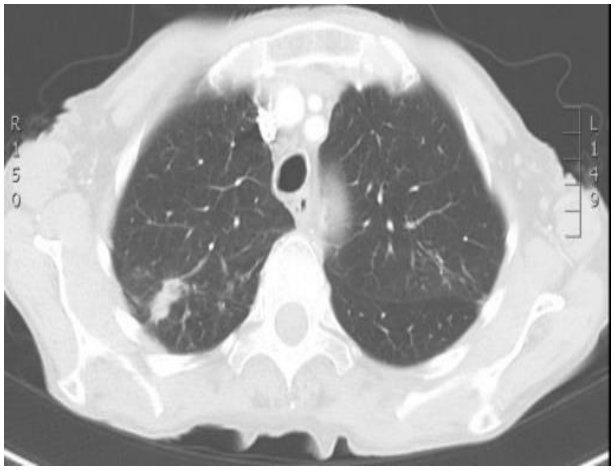

Figure 5: *HRCT chest axial (July 2020) showing an additional bilobular lesion in the posterior segment of the right upper lobe measuring 2.1 x 0.9cm.*

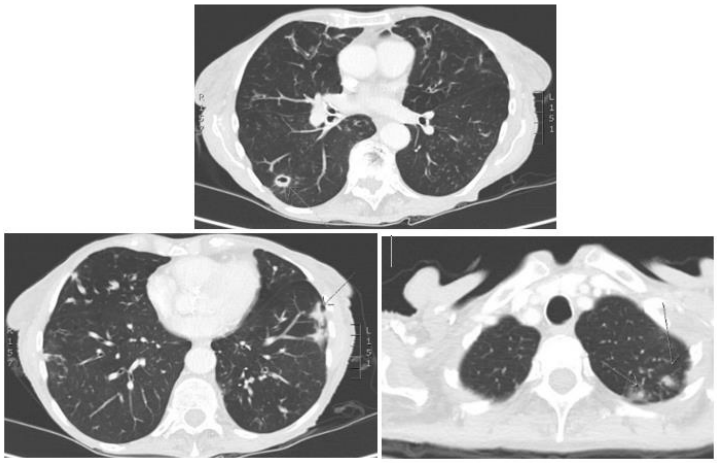

Figure 6: *HRCT chest axial (February 2021) shows multiple lesions scattered bilaterally with varying degrees of cavitation.*

The patient was provided a script for amoxicillin and clavulanic acid for two weeks, however only completed ten days in total. She was reviewed in clinic two months after treatment. Follow-up HRCT displayed progressive changes with evidence of additional cavitating lesions that had increased in wall thickness. Enlarged mediastinal lymph nodes were also noted. Repeat bronchoalveolar washings (collected in May 2021) yielded identical results and the patient reported no improvement in her symptoms. A second trial of amoxicillin and clavulanic acid was trialled to curb further growth of the cavities and attempt to eradicate *E. Coli* from her lower respiratory tract. This has proved unsuccessful to date and the next phase of treatment step will involve admitting the patient to hospital and trialling a course of intravenous antibiotics. It should be noted that the intensity of antibiotic treatment in this patient was limited by her renal function, age, and low body weight.

Discussion

Schneer et al conducted a prospective cohort study over seven years to measure the incidence of *E. coli* isolated from respiratory secretions in 177 712 patients hospitalised or reviewed in outpatient departments between 2009 and 2016. For every 10,000 secretions screened, only 4.5 returned positive cultures for *E. coli*. The Tillotson et al. study researching pneumonia and its causative organisms found that among 1882 subjects, *E. Coli* was responsible for a mere 0.7% of cases [4-7]. In the majority of patients returning positive cultures there was a degree of immunosuppression or associated comorbidity including diabetes mellitus, chronic alcoholism, malignancy, cirrhosis, or a chronic respiratory disease [8,9]. These studies emphasise the infrequency of *E. coli* as an aetiological factor in pulmonary infections.

E. coli may localise to the respiratory tract via hematogenous dissemination from a primary infection in the urogenital or intra-abdominal compartments, or via aspiration of oropharyngeal secretions [10]. Our patient initially suffered from a urinary tract infection confirmed with urine culture growing *E. Coli*. It is suspected that *E. Coli* disseminated from the bladder and deposited in the patient's damaged lung tissue secondary to longstanding bronchiectasis. The bladder has three main defence mechanisms including the uroepithelium which acts as a physical barrier, Tamm-Horsfall proteins which prevent bacterial colonization, and urine flow to promote continuous pathogen clearance [11]. Haematogenous dissemination occurs when *E. coli* adheres to receptors in the bladder epithelium, subsequently colonizing and invading the mucosal surface. Upon invasion of the uroepithelium, *E. coli* releases toxins and proteases enabling it to overcome host defences and cross the tubular epithelial barrier, thus resulting in bacteraemia [12]. The degree of bacteraemia depends on host factors such as the urine flow rate, immune status, and ammonium concentration [13]. In our patient with bronchiectatic changes, it is possible that *E. Coli* harboured the scarred lung tissue causing the pulmonary cavities however further research into this pathophysiology is required.

Radiologically, cavitating lesions with a wall thickness greater than or equal to 4mm are classified as thick-walled cavities. They may be focal, multifocal, or diffusely spread on chest imaging [1]. Differentials considered in the work-up for this patient included more common causes of lung cavitation such as fungal or atypical mycobacterium fostered by underlying bronchiectasis, metastatic

disease secondary to a squamous carcinoma or lymphoma, pulmonary Koch's, pulmonary lymphangioleiomyomatosis, and pulmonary Langerhans cell histiocytosis [12]. This patient's diffuse cavitation pattern is similar to the presentation of pulmonary Koch's of mycobacterium tuberculosis. Additionally, the progression from nodule to cavitation associated with centrilobular nodules in a 'tree in bud' pattern is typical of non-tubercular mycobacteria (NTMB). As such, an atypical mycobacterium was at the forefront of our differentials prior to the return of negative acid-fast bacilli and QuantiFERON-TB results [1]. There is inconclusive evidence as to whether *E. coli* has a pathogenic role in causing damage to lung parenchyma or conversely, if *E. coli* has propensity to inhabit diseased lung [8]. Nonetheless, we believe this patient's background of bronchiectasis was a significant contributing factor to *E. coli* migrating to the susceptible lung parenchyma and causing diffuse cavitation [13-15].

The solitary nodule in our patient's right upper lobe was stable over two years (2011-2013) as monitored radiologically. Five years later (2018) she represented with evidence of numerous nodules which were scattered bilaterally and with many showing some degree of thick-walled cavitation. Urine cultures in 2018 returned positive for *E. coli* growth and the patient was symptomatic with signs of bacteraemia, although this was not confirmed through formal blood cultures. Therefore, we postulate that the seeding of *E. coli* in the lungs was due to a long term undiagnosed urinary tract infection since 2011 with *E. Coli* as the infecting organism harbouring the bladder and undergoing hematogenous dissemination causing bacteraemia [9].

It is hypothesised that our patient's history of bronchiectasis was a major influence for *E. Coli's* residence in the lower respiratory tract. Bronchiectasis is a condition caused by ongoing airway inflammation as a result of infection, autoimmune disease, drugs or a pathogenic insult [16]. Continuous inflammation results in scarring of smooth muscle and cartilage soft tissue producing airways which are thickened and dilated [17]. For a diagnosis of bronchiectasis, chest radiography is required with HRCT as the gold standard imaging modality. The advantages of HRCT here is that it is a non-invasive technique which can provide signs suggesting bronchiectasis such as a tree in bud pattern as is the case in our patient. The tree in bud appearance is caused from a build-up of mucous debris along with simultaneous gas trapping [18]. Cystic bronchiectasis was a differential we excluded early due to no change in the lesion's air volume as interpreted across different CT slices [15]. We concluded that our patient's lesions were indeed cavitations which was a rare situation [19]. We also considered pneumatoceles which are lesions also developing post infection and appearing on chest imaging approximately 5-7 days after the initial infection [20]. Interestingly, chronic pneumatocele formation is typically associated with Buckley-Job Syndrome which is a condition predisposing a patient to multiple pathogens such as *E. Coli.* However, our patient's lesions had a wall thickness greater than 4mm thus excluding pneumatoceles. Furthermore, our research showed that the incidence of *E. Coli* causing pneumatoceles is incredibly rare with only a single published case on the phenomenon [21].

Conclusion

In summary, this case describes an atypical cause of cavitating pulmonary nodules. Although there are a multitude of diseases that present in this manner, persistent infection with *E. coli* is an etiology rarely observed. Therefore, despite the numerous cultures that returned positive for *E. coli*, ambivalence around the true causative pathogen remains. As proposed by our infectious disease consultant, it is possible that the robust growth of gram-negative bacteria has prevented detection of other underlying pathogens. Further research and case reports are required to understand the pathophysiology of this chronic infection and its implications on pre-existing pulmonary conditions.

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