Wheeze in the time of COVID-19: overcoming obstacles to an unusual diagnosis

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ABSTRACT

This case is an example of a rare cause of a common clinical presentation (persistent lobar collapse with wheeze). We describe patient management from primary care through to a national thoracic referral centre. We highlight the importance of objective testing to support an asthma diagnosis and the need to consider alternative or additional diagnoses if a patient does not respond to treatment or the clinical course is unexpected. We highlight the importance of follow-up X-ray to determine whether atelectasis has resolved, which was significantly delayed in this case due to COVID-19 restrictions. Though rare, an endobronchial tumour should be considered if atelectasis persists and when planning endoscopy for a presumed foreign body, especially if the clinical history and patient factors make a foreign body less likely. Greater awareness of this as a differential may expedite diagnoses for patients in future. We show how virtual, multicentre, multidisciplinary meetings can aid rapid diagnosis, surgical planning and coordination of follow-up across centres.

MB, PAEDIATRIC SPECIALIST TRAINEE

A previously well 11-year-old girl presented to primary care, with abrupt onset of shortness of breath and wheeze. She had a history of infantile eczema and her mother had childhood asthma and hay fever. In primary care, she was diagnosed with asthma and prescribed salbutamol, beclomethasone and montelukast, with little improvement. Nine months later, she was admitted via the emergency department of a district general hospital with an exacerbation of symptoms. She was systemically well with no fever or oxygen requirement but a persistent cough. She was noted to have bilateral polyphonic wheeze, reduced breath sounds and crackles at the right base with dull percussion notes. Her radiograph of the chest (figure 1A) showed dense right middle and lower lobe collapse. She received salbutamol and a short course of oral clarithromycin and prednisolone.

After 2 weeks, her symptoms had not resolved with reported daily wheeze. No wheeze was heard on auscultation but she coughed throughout the consultation and was switched to inhaled fluticasone. A month later, despite symptomatic improvement, crackles and reduced breath sounds were still heard at the right base. Repeat radiograph of the chest showed persistent right middle and lower lobe collapse, therefore a 2-week course of coamoxiclav was prescribed. Her subsequent planned follow-up and her repeat radiograph of the chest (essential in ensuring atelectasis had resolved) was cancelled due to the COVID-19 pandemic. Seven months later, a recurrence of shortness of breath on exertion and wheeze, associated with fever and haemoptysis prompted review. These worsening symptoms, combined with an absence of radiological improvement, led to a tertiary respiratory referral.

ARS, CONSULTANT RESPIRATORY PAEDIATRICIAN AND MD, CONSULTANT PAEDIATRIC OTORHINOLARYNGOLOGIST

Initial results showed a microcytic, hypochromic anaemia with raised white cells. Immune workup showed suboptimal *Haemophilus influenzae* type B antibodies but was otherwise normal. Examination revealed no wheeze or crackles but bronchial breathing at the right base. Given the persistent atelectasis, it was important to exclude an inhaled foreign body, although the team acknowledged this would be less likely in a neurologically intact older child with no history of choking. Foreign body aspiration can, however, mimic other illnesses such as asthma or pneumonia and diagnosis can be delayed.

Rigid bronchoscopy is traditionally the preferred intervention for suspected foreign body aspiration with high reported success rates.[1] Flexible bronchoscopy has been suggested, as first line, if the evidence of foreign body aspiration is less convincing[2]; however, success rates for foreign body removal with flexible bronchoscopy are variable.[1] A secure airway, with a laryngeal mask or endotracheal tube, is strongly recommended and rigid bronchoscopy should be available immediately in the event of difficult extraction or complications.[1]

We proceeded with joint rigid and flexible bronchoscopy by the ear, nose and throat and respiratory teams. This revealed a mass in the bronchus intermedius, close to the right main bronchus (figure 1B), thought to be granulation tissue obscuring a foreign body. Attempts to remove the obstruction with biopsy forceps failed and so this initial endoscopy was abandoned, with a plan to repeat the procedure after systemic antibiotics and corticosteroids. Though rare, an endobronchial tumour was an important differential diagnosis given the persistent atelectasis, rarity of foreign body in this age group and findings on bronchoscopy.

MB, PAEDIATRIC SPECIALIST TRAINEE

A CT of the chest, initially booked to follow the bronchoscopy, was postponed to enable assessment of the right middle and lower lobes after removal of the obstruction. The long history of

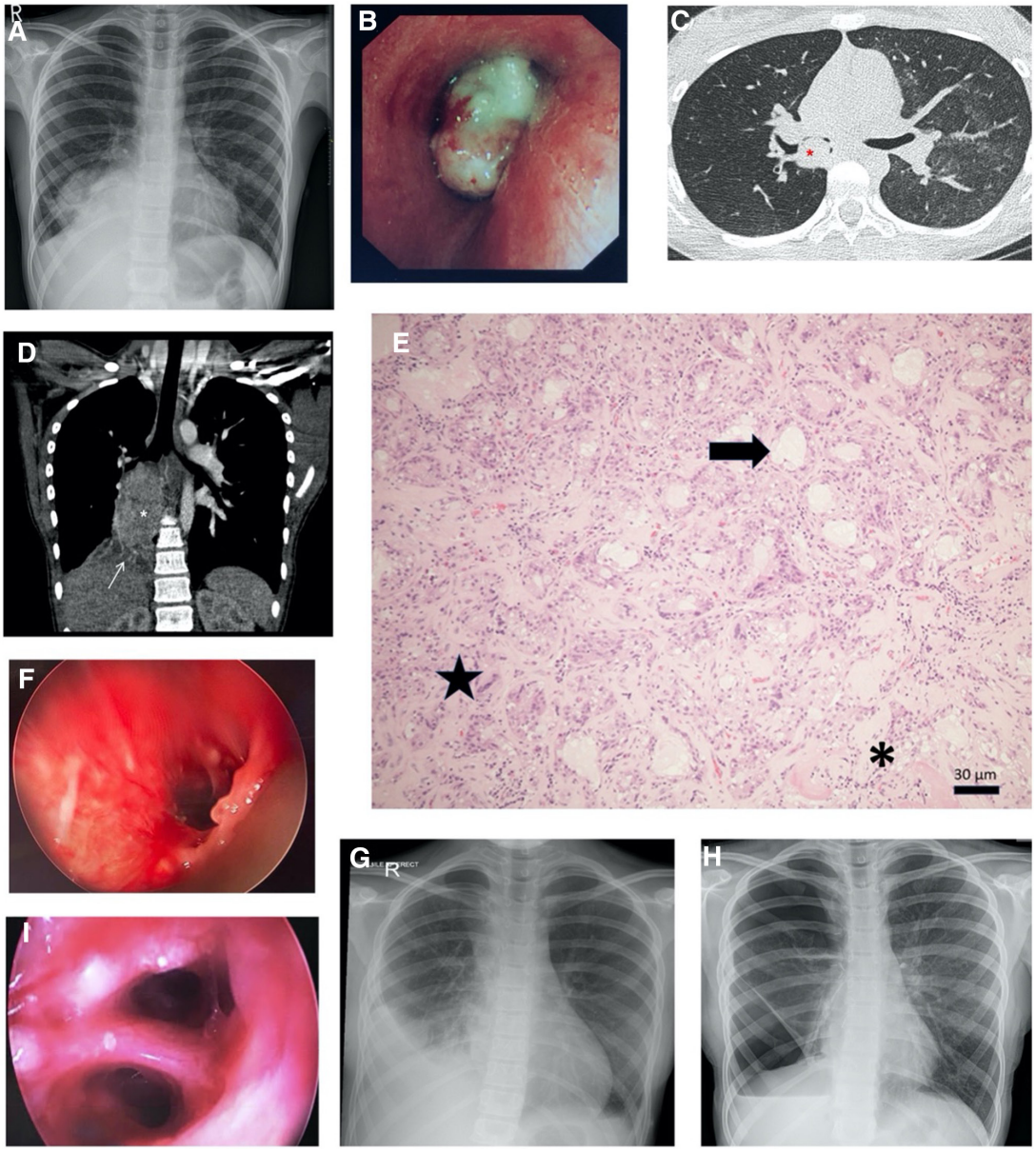

Figure 1 (A) Radiograph of the chest with dense right middle and lower lobe collapse. (B) Mass in the bronchus intermedius, close to the right main bronchus, seen on bronchoscopy, thought to be granulation tissueobscuring an underlying foreign body. (C) Axial CT section on lung window settings demonstrates the mass within the bronchus intermedius (*) and patchy ground glass opacification in the left lung (in keeping with aspirated blood from recent haemoptysis). (D) Coronal reconstruction on soft tissue windows from postcontrast CT demonstrates an enhancing soft tissue mass (*) with mucoceles within the obstructed bronchi distal to the mass (linear low attenuation areas indicated with an arrow). (E) Tumour with predominantly tubular architecture composed of mildly atypical clear (asterix), mucinous (arrow head) and squamoid (star) cells, in keeping with low grade mucoepidermoid carcinoma (H&E, ×100). (F) Bronchoscopy image immediately after resection to ensure patency. (G) Radiograph of the chest following removal of right-sided chest drain showing moderate sized pleural effusion. (H) Radiograph of the chest just over 3 weeks postoperatively showing right hilar surgical clips and a large right-sided hydropneumothorax. (I) Follow-up bronchoscopy 5 months postoperatively showing fully opened bronchus with no granulomas.

collapse increased the risk of progression to bronchiectasis.[3] The histology from this initial bronchoscopy showed inflammatory granulation tissue. Microscopy and culture from the bronchoalveolar lavage samples were positive for *Neisseria*, *Streptomyces* and *Gemella* sp, which were described as mixed upper respiratory tract flora and not thought to be pathogenic. The samples were negative for tuberculosis, fungi and SARS-CoV-2 coronavirus.

ARS, CONSULTANT RESPIRATORY PAEDIATRICIAN AND MD, CONSULTANT PAEDIATRIC OTORHINOLARYNGOLOGIST

A second bronchoscopy was performed after 1 week of intravenous coamoxiclav, dexamethasone for 48 hours prior to the procedure and cautious chest physiotherapy. The mass was again visualised in the same position and a balloon catheter was advanced beyond it, inflated and withdrawn in an unsuccessful attempt to dislodge it. The mass was debulked and sent for

further histology. The rare diagnosis of an endobronchial tumour was now thought more likely. A virtual multidisciplinary team meeting enabled sharing of information, images and opinion, which expedited referral and transfer of the patient to a national referral centre.

TS, CONSULTANT RADIOLOGIST IN PAEDIATRIC AND ADULT CARDIOTHORACIC IMAGING

The initial radiograph of the chest (figure 1A) shows a blunted right costophrenic angle, easily misinterpreted as a pleural effusion. The absence of a visible horizontal fissure, however, in combination with a dense triangular lower lobe collapse and separate superimposed density is in keeping with right middle and lower lobe collapse. The blunted costophrenic recess is secondary to upper lobe hyperexpansion, filling the lost space. This appearance, highly suggestive of a bronchus intermedius obstruction, should prompt further investigation. Where a mass is a possibility, contrast injection is extremely useful. CT performed at our centre showed a mass in the bronchus intermedius, which enhanced avidly, but did not demonstrate calcification or any further differentiating feature (figure 1C,D). More common entities with an enhancing mass include inflammatory myofibroblastic or carcinoid tumours, but, although very rare at this age, a more malignant tumour should always be considered.

AR, CONSULTANT THORACIC AND CARDIOTHORACIC TRANSPLANT PATHOLOGIST

Both biopsies taken at the tertiary centre were initially reported as inflammatory granulation tissue. A second opinion from a histopathologist at the national referral centre on the tissue from the second biopsy concluded that although the appearances were atypical, the material was not suitable for diagnosis. A further biopsy performed at the national referral centre showed fragments of inflamed and ulcerated mucosa infiltrated by tumour composed of tubules and solid nests of tumour cells. The tumour cells comprised a mix of mildly atypical clear, mucinous and squamoid cells (figure 1E). The stroma showed hyalinisation and focal areas of calcification. There was no necrosis or mitosis. The appearances were consistent with low grade mucoepidermoid carcinoma (MEC). Cytogenetic studies confirmed the presence of an MAML2–CRTC1 fusion, which is characteristic of these tumours.

Primary lung tumours are rare in children, accounting for <1% of new childhood cancer diagnoses annually. MEC accounts for 9%–10% of primary lung malignancies in childhood and adolescence, with pleuropulmonary blastomas, carcinoid tumours and bronchogenic carcinomas comprising the majority of the rest.[4] Paediatric MEC is mainly described in case reports and case series. Pulmonary MEC is typically an exophytic polypoid mass arising from submucosal bronchial glands that develops along the tracheobronchial tree and causes bronchial obstruction. The tumour is strongly associated with a t(11;19) translocation, commonly involving CRTC1 and MAML2. Tumours can be graded into low, intermediate and high grades, based on a number of grading systems, the more commonly used being the WHO and Brandwein grading systems.[4] Both are based on assessment of the predominant cell type, architecture and presence of aggressive features including mitotic count, nuclear atypia, necrosis and invasive spread.

SJ AND SB, CONSULTANT THORACIC SURGEONS

Following the diagnosis of MEC, we used the radiology images to plan surgery. At operation, we found the tumour was completely blocking the bronchus intermedius. We performed a right middle and lower lobectomy with sleeve reimplantation of the right upper lobe bronchus, in order to achieve clear margins but avoid a pneumonectomy. Bronchoscopy immediately post resection ensured bronchus patency (figure 1F). Resection with negative margins is the mainstay of treatment for tracheobronchial MEC and is mostly curative, with adjuvant chemotherapy or radiotherapy reserved for recurrence. Prognosis in young people, where the majority of cases are low grade, is generally excellent. Our surgical approach was to achieve complete resection of the tumour but preserve as much lung parenchyma as possible. This will optimise prognosis, while minimising long-term sequelae associated with pneumonectomy such as kyphoscoliosis or functional limitations.

MB, PAEDIATRIC SPECIALIST TRAINEE

A right-sided chest drain was removed 2 days after surgery and her subsequent radiograph of the chest showed a moderate sized pleural effusion (figure 1G). A virtual multidisciplinary meeting, involving both the local tertiary centre and the national referral centre, allowed careful planning of follow-up for safe discharge 4 days after surgery. Just over 3 weeks postoperatively, a pneumothorax was detected at local follow-up (figure 1H). Again, virtual conferencing facilitated planning and she was readmitted to the national referral centre for video-assisted thoracoscopic surgery and drain insertion, which was placed on suction. She was discharged a week later with the drain and a Heimlich valve in situ, necessitated by a persistent pneumothorax. This was removed after 16 days, following radiological resolution of the pneumothorax.

She continues to be followed up by respiratory, oncology and surgical teams at both the tertiary hospital and national referral centre but is expected to make a full recovery. Her respiratory symptoms have resolved. She is back at school full time and is participating in sports. Her follow-up bronchoscopy showed a complete patent right main bronchus to upper lobe bronchus, and an end-to-end partially telescoped anastomosis (figure 1I).

AB, PROFESSOR OF PAEDIATRICS AND PAEDIATRIC RESPIROLOGY

This young woman's 'asthma' symptoms may have been due to fixed airway narrowing, related to her endobronchial tumour. Atypical features include sudden onset, persisting chest radiograph abnormalities and poor response to initial treatment. In these circumstances, alternative diagnoses should be considered including inhaled foreign body and rare diagnoses such as endobronchial tumour. Greater awareness of an endobronchial tumour as a differential diagnosis, especially in a context where inhaled foreign body is unlikely, may expedite diagnoses and thus appropriate treatment for patients in future.

As recommended in the National Institute for Health and Care Excellence guidelines, objective testing would have helped confirm or refute the diagnosis of asthma and would comprise spirometry (with bronchodilator reversibility), combined with measurement of exhaled nitric oxide.[5] Although debate exists regarding the role of spirometry in paediatric asthma diagnosis,[6] a demonstration of fixed airways obstruction may have prompted earlier consideration of alternative diagnoses in this patient. At the time of subsequent follow-up, these procedures were considered aerosol generating in the hospital trusts in which the patient was treated and so spirometry was not performed as the precautions then thought to be necessary were not yet in place to ensure safety due to COVID-19.

A lack of response to multiple courses of antibiotics makes uncomplicated bacterial pneumonia unlikely and should prompt clinicians to look for other underlying causes in an afebrile, non-septic child. Follow-up was interrupted and her diagnosis and treatment were delayed by the COVID-19 pandemic due to cancellations. Crucially, her follow-up X-ray of the chest was cancelled; follow-up radiographs are paramount to ensure atelectasis has resolved.

Despite the challenges faced, the COVID-19 pandemic also brought opportunities for improved coordination of care. The use of virtual conferencing software has enabled multidisciplinary team meetings across centres to share radiology images, histology and expertise. This has facilitated communication and the coordination of care in reaching a diagnosis, planning for surgery and follow-up thereafter.

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