Pneumonia and parapneumonic pleural effusions in adults with cystic fibrosis

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To the Editor:

Cystic fibrosis (CF) is caused by an absence or dysfunction of the transmembrane conductance regulator (CFTR) protein, an anion channel exchanging chloride and bicarbonate across epithelia. In the airways, this ionic imbalance results in dehydrated airway surface liquid, tenacious secretions and impaired mucociliary clearance, leading to endobronchial infections, inflammation and progressive lung damage [1].

Endobronchial inflammation in CF is characteristically neutrophilic with an elevation in neutrophil elastase and other pro-inflammatory biomarkers including IL-8, TNF-α, IL-1β, IL-6 and calprotectin. In addition, CF monocytes and airway epithelial cells have an innate exaggerated NLRP3 inflammasome response to lipopolysaccharide from Gram-negative bacteria, such as *Pseudomonas aeruginosa*. This combined with suboptimal neutrophil antimicrobial activity and macrophage bacterial killing, contribute to progressive lung damage [2–6]. Highly effective CFTR modulators (HEMT) partially downregulate, *in vivo*, this chronic innate hyperinflammation, while significantly improving lung physiology [7–9].

Clinically, CF is associated with endobronchial infections, mucus plugging, and bronchiectasis. Radiological pneumonia with or without parapneumonic effusions is a relatively uncommon presentation in adults with CF, although autopsy examination demonstrates features of pneumonia in addition to known airway involvement [10]. It is conceivable that the aberrant inflammatory and hyper-immune response in CF could hinder the spread of infection to the lung parenchyma and pleural spaces. If this was the case, then the partial normalisation of lung physiology and inflammatory profile with HEMT could potentially increase the frequency of pneumonia in people with CF.

There are presently limited data on the prevalence of pneumonia and pleural effusions in immune-competent adults with CF. In this case series, we describe the presentation, treatment and outcomes of pneumonia and parapneumonic effusions in a large cohort of adults attending a regional CF centre.

A retrospective study was performed, extracting data from the Leeds adult CF electronic patient records, which was established in 2006–2007. All READ and SNOMED CT codes relating to pneumonia, pleural effusions, parapneumonic effusion and empyema were identified in a cohort of 600 patients, between 1 January 2007 and 31 December 2023. Exclusion criteria included solid organ transplant (SOT) and pneumonia having occurred in childhood. All patients had provided prior written consent for their clinical data to be used for research purposes. Informed consent was obtained for reproducing patients' imaging.

26 cases (4.3% of the cohort) of pneumonia and/or pleural effusions were identified. 12 cases were excluded as post-SOT, and four were excluded as pneumonia occurred in childhood.

A total of 10 subjects were included in this series. Baseline characteristics are summarised in figure 1a. The population was predominantly male (n=7) and F508del homozygous (n=9), 7 patients produced *P. aeruginosa* and 1 *Burkholderia multivorans*. Median age at presentation was 29.5 (IQR27–44)) with variable severity of lung disease (best forced expiratory volume in 1 s % predicted in the 12 months prior to the diagnosis of pneumonia was 52 (37.5–66)), with 7 (70%) having moderate-to-severe lung disease.

Shareable abstract (@ERSpublications)
Pneumonia and parapneumonic effusion are uncommon in adults with CF. Clinical presentation and recovery may change following introduction of CFTR modulators (HEMT). Further prospective studies are needed. https://bit.ly/3BktB2N

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a)

	All (n=10)	Pre-HEMT (n=6)	On HEMT (n=4)
Age (y)#	29.5 (27–44)	27.5 (23.5–43)	35.2 (27.3–45.2)
Male sex	7 (70%)	4 (66.7%)	3 (75%)
F508del			
Homozygous	9 (90%)	6 (100%)	3 (75%)
Heterozygous	1 (10%)		1 (25%)
FEV_1 % pred¶	52 (37.5–66)	44.5 (34–77)	75 (53.5–105)
BMI	21.6 (20.56–23.3)	21.4 (20.5–22.76)	23.7 (20.5–26.4)
Microbiology			
P. aeruginosa	7 (70%)	5 (83.3%)	2 (50%)
B. multivorans	1 (10%)	1 (16.7%)	

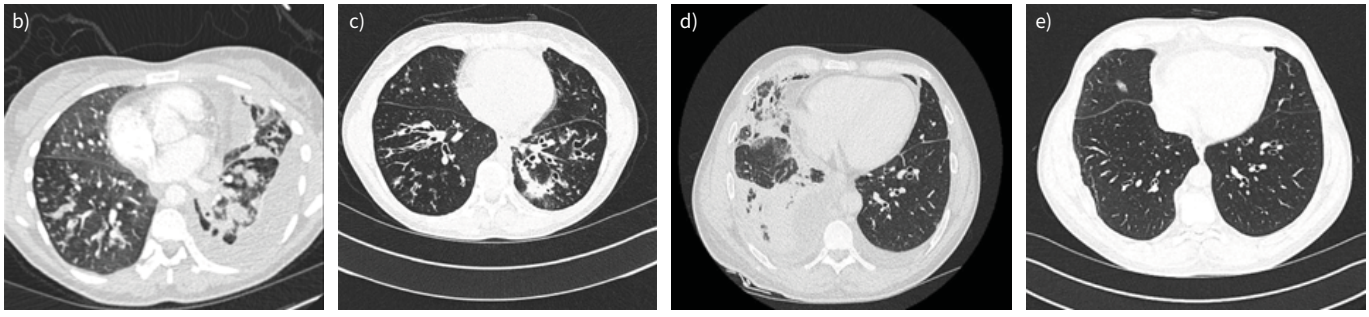

FIGURE 1 a) Baseline characteristics of the population. Data are presented as median (interquartile range) or n (%). b) and c) Consolidative changes and parapneumonic effusion in an adult with cystic fibrosis pre-modulator. c) Repeated computed tomography scan after 4 months showing persistent, but improved, consolidative changes and thickening of the pleura. d) and e) Consolidative changes and parapneumonic effusion secondary to Streptococcal infection in an individual with cystic fibrosis on HEMT. e) Repeated computed tomography scan after 4 months shows complete resolution of the parenchymal changes and residual minimal pleural thickening. HEMT: highly effective modulator therapy; FEV_1: forced expiratory volume in 1 s; BMI: body mass index; *P. aeruginosa*: *Pseudomonas aeruginosa*; *B. multivorans*: *Burkholderia multivorans*. #: at diagnosis of pneumonia; ¶: Best FEV_1 in the 12 months prior to pneumonia.

Six cases of pneumonia, four of which were associated with parapneumonic effusions, occurred prior to the introduction of HEMT. One case was a post-operative aspiration pneumonia, and one case of effusion was an incidental finding complicating a pulmonary embolism. All patients presented with increased respiratory symptoms and pleuritic chest pain, but none were pyrexial. Risk factors included diabetes (n=1), cirrhosis (n=1) and prolonged steroid treatment (n=2).

Post HEMT, there were four cases of pneumonia, two of which were associated with parapneumonic effusions. All patients had been established on treatment for a prolonged period of time (average time on treatment 29.5 months). Pyrexia occurred in all (n=4). Two cases were associated with viral infections (flu n=1 and COVID n=1) and one occurred in an individual who was HIV-positive but had no detectable viral load and normal lymphocyte count.

Diagnosis of pneumonia and parapneumonic effusion was confirmed with multimodal imaging including chest radiograph (n=10), computed tomography (n=5) and ultrasound scan (n=5). Sputum analyses were positive for the patients' usual colonising pathogens. Blood cultures were sent in all pyrexial patients, with one positive for *Streptococcus pneumoniae* in a patient on HEMT.

Overall, there were six cases of parapneumonic effusion, five of which required pleural aspiration and chest drain. Pleural fluid analysis revealed an inflammatory exudate with fluid pH ranging from 6.88 to 7.3. Pleural fluid cultures were positive in two cases and isolated *P. aeruginosa* and *S. pneumoniae*, pre- and post-HEMT respectively. In two cases post-HEMT, the resolution of parapneumonic effusion required the intrapleural administration of tissue plasminogen activator and DNase according to the MIST-2 protocol [11].

All patients required hospital admission and prolonged IV antibiotic treatment (mean duration was 3.7 weeks (range 2–6)), which produced clinical improvement and fall in infection markers. Radiological

resolution was achieved in seven patients, with one case of life-threatening empyema resulting in mild persistent pleural thickening (figure 1 panels d and e).

In line with the current literature, pneumonia and parapneumonic effusions in adults with CF are infrequent [12–14]. Presentation appears to differ in subjects on HEMT. While all cases of parapneumonic effusions were associated with acute pleuritic chest pain, pyrexia was only present in those on HEMT.

In our cohort, chest radiographs were routinely undertaken on hospital admission and in all those experiencing pleuritic or unexplained chest pain to rule out pneumonia and other CF-associated complications, and are formally reported by a radiologist. This would suggest that the low prevalence of consolidations and effusions, seen in this adult cohort, is likely to be a true reflection of clinical presentation. However, small, uncomplicated parapneumonic effusions might have been missed in the absence of routine computed tomography of the chest.

In previous reports, parapneumonic effusions have been associated with an immunocompromised status such as SOT, poorly controlled diabetes, cirrhosis or long-term systemic steroids [12–14]. There has also been a link between parapneumonic effusions, older age and advanced lung disease, an association also seen in the present cohort [14].

Pyrexia seemed to be a feature in patients on HEMT, with two cases complicating viral infections and one case being caused by severe streptococcal infection.

Impaired host immunity is associated with microbial translocation from airways to lung parenchyma and pleural space. Theoretically, the low prevalence of parapneumonic effusion in adults with CF may reflect host and pathogen interactions, combined with heightened immunological and inflammatory responses.

Defective CFTR also appears to reduce cell migration, proliferation, epithelial repair and epithelial mesenchymal transition [15], a process which may be partially reversed by HEMT. We were surprised by the unexpected, dramatic and relatively rapid improvement in lung parenchymal changes in those on HEMT. This may suggest a potential enhancement in reparative and regenerative processes in the CF lung following partial restoration of epithelial CFTR function.

While data collection did benefit from the routine use of prospective diagnostic coding within the CF electronic patient records, which enabled the accurate identification of clinical cases, study limitations include the retrospective and single-centre design and the small number of patients, which did not allow for the assessment of meaningful clinical correlations. Large multicentre or registry studies might help clarifying whether clinical status or specific colonising pathogens affect the clinical outcome in the event of complications such as pneumonia and/or parapneumonic effusion occur. While CT scans were not routinely undertaken to screen for pneumonic changes and pleural effusions in our cohort, conventional chest radiographs have been routinely undertaken, reflecting real world practice.

Pneumonia and parapneumonic effusion appear to be uncommon in adults with CF. Risk factors should be assessed and early and appropriate antibiotic and supportive treatment given to maximise the restoration of lung function and resolution of parenchymal changes. The clinical presentation of pulmonary exacerbations may change following HEMT. Further prospective studies are needed.

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