An asthma phenotype comprising bronchial wall thickening and mucus plugging confers worse clinical outcomes

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Letters

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Precision medicine in asthma refers to the collection of a wide array of data including clinical, biomarker, radiological, lifestyle, and genetic information to optimize patient outcomes. It involves the identification of treatable traits that can be targeted to produce better results compared with conventional care. Our aim was to investigate the impact of a particular phenotype, dual bronchial wall thickening (BWT) and mucus plugging (MP), detected on high-resolution computed tomography (HRCT) imaging, on spirometry, type 2 (T2) biomarkers, and exacerbation frequency in patients with poorly controlled asthma. We chose this combination phenotype because there have been recent studies looking at the effect of biologics on both BWT and MP individually, but not together. The hypothesis was that the dual MP-BWT phenotype confers worse clinical outcomes than either phenotype alone.

Data on 62 patients, diagnosed by respiratory physicians to have poorly controlled persistent asthma as defined by the Global Initiative for Asthma, and who had BWT, MP, or both detected on HRCT were retrospectively collected between January 2016 and March 2022. Patients with concomitant chronic obstructive pulmonary disease or bronchiectasis were excluded. Blinded to all clinical data, a senior thoracic radiologist measured MP using methods described previously.[1] Briefly, an MP score of at least 1 (maximum score 20) was considered positive for MP. There were 2 senior thoracic radiologists who independently measured the airway lumen and total airway area at 4 different bronchopulmonary segments, namely: (1) right apical, (2) right lower lobe posterior basal, (3) left apicoposterior, and (4) left lower lobe posterior basal. Wall area percentage measurements were subsequently calculated by dividing wall area by total airway area and expressed as a percentage.[2] Intraobserver and interobserver interclass correlations (95% confidence interval) relating to airway lumen and total airway measurements amounted to 0.90 (0.86-0.93, $P < .001$) and 0.81 (0.54-0.90, $P < .001$) respectively. A pooled wall area percentage was determined and considered positive for BWT when exceeding the median value of 50%. The HRCT scans were performed in volumetric mode with maximal inspiration, as per standard department protocol (128-slice CT Revolution EVO, GE Healthcare). HRCT scans were performed within 1 year of pulmonary function testing, exacerbation, and asthma control data.

Spirometry (Micromedical, Chatham, United Kingdom) was performed according to European Respiratory Society/American Thoracic Society guidelines. NIOX VERO (Circassia, Oxford, United Kingdom) was used to measure fractional exhaled nitric oxide (FeNO) according to the manufacturer's instructions and American Thoracic Society guidelines. A 6-point asthma control questionnaire (ACQ) was used to assess disease control and the number of severe exacerbations requiring at least a 5-day course of oral prednisolone 40mg/day was retrieved from medical records. All measurements were taken before patients started biologic therapy. The presence of nasal polyps (NP) was determined by endoscopy in patients with a suggestive history of nasal symptoms.

Statistical analysis was performed using Statistical Package for the Social Sciences version 28. Data were assessed for outliers and normality with Shapiro-Wilks before analysis. Independent *t* tests were implemented to detect differences in spirometry and ACQ, whereas Mann-Whitney *U* tests were used for exacerbation frequency, T2 biomarkers, BWT, and MP scores with a 2-tailed alpha error of .05. Categorical variables were analyzed with $\chi 2$ chi-squared tests. Carestream Vue Picture Archiving and Communication Systems software were used to obtain MP and airway wall thickness measurements. Caldicott guardian approval (IGTCAL10360 and IGTCAL10810+) was obtained before any data collection.

Demographic data are presented in Table 1. Patients with dual presence of BWT and MP were older and more likely to exhibit concomitant chronic rhinosinusitis with NP. Both groups had a similar prevalence of severe asthma as defined by the Global Initiative for Asthma.

The dual BWT-MP phenotype had significantly worse airflow obstruction as forced expiratory flow rate between 25% and 75% of forced vital capacity ($FEF_{25-75\%}$) and the ratio of forced expiratory volume in 1 second to forced vital capacity. The dual phenotype was accompanied by significantly greater peripheral blood eosinophils (PBE) and FeNO in conjunction with more frequent severe exacerbations compared with either BWT or MP alone (Table 1). There were no differences in the ACQ scores.

In a recent retrospective observational study (n = 16), it was found that MP was spatially associated with BWT in severe asthma.[3] From a pathophysiological standpoint, interleukin (IL)-13 governs both airway smooth muscle and mucus hypersecretion. Therefore, up-regulation of IL-13 signaling may play a key role in the development of the dual BWT-MP phenotype. Such a hypothesis is supported by higher FeNO levels, which are in turn regulated by IL-13. However, to explore this important question further, we await the results of the ongoing study (NCT04400318) investigating the impact of the anti-IL4Rα biologic dupilumab that suppresses both IL-13 and IL-4 signaling on BWT and MP, albeit both as secondary outcomes.

We observed a mean absolute difference in FEF_{25-75} of 0.63 L/s, which exceeds the biological variability of 0.21 L/s in patients with severe asthma.[4] The FEF_{25-75} is a measurement of volume-dependent small airway closure and is more sensitive than forced expiratory volume in 1 second in detecting therapeutic response.[5] Notably, here an additional jeopardy was detected with the dual BWT-MP phenotype compared with either BWT or NP alone, especially because both pathologies are independently associated with worse lung function.[1] There were also

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Table 1
Differences in Demographics, Spirometry, Asthma Control, Type 2 Biomarkers, and Exacerbation Frequency

Characteristic	BWT or MP (n = 39)	BWT and MP (n = 23)
Sex (F/M)	32/7	14/9
Age (y)	46 (41-50)	59 (53-65)[a]
BMI (kg/m^2)	31.6 (28.6-34.5)	29.4 (27.2-31.7)
ICS dose (μg)	1795 (1667-1922)	1830 (1675-1985)
Asthma severity (%)	85%	87%
Current smoker (%)	18%	4%
LABA (%)	82%	96%
LAMA (%)	62%	65%
LTRA (%)	56%	74%
OAH (%)	62%	52%
Nasal polyps (%)	13%	57%[a]
FEV_1 (%)	82.0 (74.4-89.6)	73.3 (63.4-83.2)
FEF_{25-75} (%)	50.4 (40.2-60.5)	35.7 (25.7-45.7)[b]
FVC (%)	100.0 (94.4-105.7)	96.9 (88.9-105.0)
FEV_1/FVC	0.69 (0.64-0.74)	0.61 (0.56-0.67)[b]
ACQ	2.6 (2.2-3.0)	2.6 (1.9-3.2)
PBE (cells/μl)	200 (300)	390 (190)[b]
FeNO (ppb)	20 (23)	31 (55)[b]
Total IgE (kU/L)	106 (384)	128 (361)
Exacerbations/y	2 (4)	4 (2)[b]
Pooled WA (%)	50.9 (9.0)	55.5 (7.0)[a]
MPS	0 (1)	4 (6)[a]

Abbreviations: ACQ, asthma control questionnaire; BMI, body mass index; BWT, bronchial wall thickness; FEF25-75, forced expiratory flow rate between 25 and 75% of FVC; F, female; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid dose as beclomethasone equivalent; IgE, immunoglobulin E; LABA, long-acting β-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; M, male; MP, mucus plugging; MPS, mucus plug score; OAH, oral antihistamine; PBE, peripheral blood eosinophils; T2, type 2; WA, wall area.
NOTE. Age, BMI, ICS dose, spirometry, and ACQ are reflected as means (95% CI) whereas T2 biomarkers, exacerbations, BWT, and MPS are reflected as medians (IQR). N equals 24 with BWT and n equals 15 with MP alone.
[a]*P* less than .001.
[b]*P* less than .05.

higher levels of FeNO and PBE associated with the dual phenotype despite both groups having a similar prevalence of severe asthma and taking comparable high mean doses of inhaled corticosteroid.

Both groups had poor symptom control denoted by high mean ACQ scores of 2.6, although the dual BWT-MP phenotype was associated with significantly more frequent severe exacerbations requiring oral corticosteroids. This apparent disconnect between symptoms and exacerbations might be explained by greater T2 inflammation because PBE and FeNO are strong predictors of asthma exacerbations.[6] In this regard, eosinophil depletion with the anti-IL5Rα biologic benralizumab has recently exhibited efficacy in attenuating both MP and BWT independently.[7,8] Our data revealed a significantly higher prevalence of chronic rhinosinusitis with NP in the dual BWT-MP group in keeping with a higher overall type 2 disease burden. Whereas it is difficult to justify exposing all patients with moderate-severe asthma to ionizing radiation, both MP and BWT can potentially be used as radiologic biomarkers to help guide biologic choice, and further research in this area is required. In the meantime, we feel that those with uncontrolled or difficult-to-treat disease despite optimal medical therapy would especially benefit from a HRCT scan.

We acknowledge that the present study contains potential limitations including its retrospective nature and the relatively small sample size from a single UK specialist severe asthma centre. However, despite this, significant associations were detected in key clinically relevant outcomes. Second, HRCT scans were not performed contemporaneously with lung function or T2 biomarkers. However, it is recognized that most mucus plugs persist over a period of at least 3 years.[9]

In conclusion, we report a unique radiologic phenotype comprising both BWT and MP, which was associated with worse airway obstruction, greater type 2 inflammation, and more frequent severe exacerbations. Future studies are now indicated to evaluate whether this dual phenotype is more responsive to biologics.

Disclosures

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