

Differences in airway wall remodelling in asthma and EB

We read with interest the study by Park *et al*¹ published recently in *Thorax*. We agree that non-asthmatic eosinophilic bronchitis (EB), a condition characterised by eosinophilic inflammation without evidence of variable airflow obstruction, is a powerful disease control group to study the mechanisms involved in the development of airway hyperresponsiveness in asthma. Previous comparative studies have shown that asthma and EB are immunopathologically similar but that there are key differences—namely, mast cell localisation to the airway smooth muscle bundle² and increased IL-13 expression in asthma. Park *et al*¹ have proposed in their recent study that this list needs to be extended to include increased airway wall area as a feature confined to asthma. This is an important observation as other HRCT studies in asthma have suggested that increased airway wall area may, in fact, protect against airway hyperresponsiveness.³ However, the observed absence of increased airway wall area in the EB group studied may not reflect distinct differences between this disease and asthma, but may simply reflect duration of disease.

The subjects with EB had participated in an earlier study.⁴ In this study duration of disease was on average about 7 months and very few subjects had symptoms or evidence of inflammation for more than 1 year. The duration of disease in the asthma group is not clear from the current study, but this is likely to be years in many cases. This point needs to be clarified as conclusions made about possible differences in remodelling between asthma and EB are undermined if the disease duration is markedly different.

In our experience, some patients with EB and prolonged eosinophilic airway inflammation have a progressive decline in their lung function,⁵ suggesting that airway wall remodelling is a feature in some patients with this condition. Whether airway remodelling and increased airway wall thickness are features shared by asthma and EB or are specific to the asthma phenotype therefore remains to be fully addressed.

S Siddiqui, C E Brightling

Institute for Lung Health, Glenfield Hospital, Leicester LE3 9QP, UK; ceb17@le.ac.uk

Competing interests: none declared.

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Multidrug resistance emerging in North London outbreak

We write on behalf of the Outbreak Control Committee (OCC) investigating an outbreak of isoniazid mono-resistant tuberculosis (TB) affecting over 260 cases (222 in London) to alert clinicians about recent transmission of a multidrug resistant (MDRTB) component with unusual characteristics.

A unique genetic fingerprint on Restriction Fragment Length Polymorphism (RFLP) typing¹ at the Health Protection Agency Mycobacterium Reference Unit (HPA MRU) has allowed tracking of the strain. Fifty percent of cases were born in the UK; they are from a wide ethnic and social background with foci in high risk groups including the homeless, injecting drug users, and prisoners.² Inhalation of crack cocaine is common and may have contributed to the spread. All outbreak cases are recommended to receive directly observed therapy (DOT) unless adherence is confirmed. Adherence to treatment has been poor in one third and several have acquired MDRTB. Some of these were active in the community while infectious, and we have seen primary MDRTB in two young people with no known epidemiological link apart from relative geographical proximity.

Of six outbreak MDR cases in London, three are distinct strains with rare mutations (D516Y, H526R, S531W) in the *rpoB* gene, demonstrable by commercial genetic probing. These were found in patients poorly concordant with treatment. A wild type genotype not detectable on commercial molecular testing routinely used in the UK³ has been found in one poorly compliant case followed by two (primary) new cases suggesting community acquisition.

The British Thoracic Society guidelines^{4,5} recommend that all TB cases are microbiologically confirmed where possible. Adequate samples should be taken before treatment and isolates sent to the HPA MRU to enable detection of outbreak cases as well as sequencing of MDRTB strains. This is necessary so that appropriate treatment can be initiated as soon as possible and enhanced contact tracing carried out for these outbreak cases.

H Maguire

Health Protection Agency (HPA), London, UK

M Ruddy

Health Protection Agency Mycobacterium Reference Unit (HPA MRU), London, UK

G Bothamley

Homerton Hospital, London, UK

the important point that airway remodelling may not reflect distinct differences between eosinophilic bronchitis (EB) and asthma, but may reflect duration of disease. There are few studies on the disease course of EB. Berry *et al*² have studied EB for more than 7 years. The most common outcome in EB is continuing disease and complete resolution is rare. Asthma and fixed airflow obstruction develop in relatively few patients. Gronke *et al*³ reported that, with a shorter duration of asthmatic disease, airway hyperresponsiveness is associated with airway inflammation whereas, with a disease of longer duration, it is associated with impaired lung function. This suggests that, in chronic asthma, ongoing changes become the primary determinant of functional characteristics.

As stated in our paper, patient data including asthma and EB were limited to a follow up period of 6–24 months. As Dr Brightling points out, at the start of the study the disease duration in patients with asthma was about 6 years while that of patients with EB was 5–8 months. EB and asthma cause significant changes in the small airways indicated by an increase in air trapping and centrilobular prominence on radiological/HRCT scans. However, the thickness of the large airway was normal in the patients with EB. We suggest that changes in the large and small airways were different between asthma and EB, indicating bronchial wall thickening in the airway hyperresponsiveness that characterises asthmatics over 2 years of follow up.

However, we agree with Dr Brightling that the duration of the disease may influence airway remodelling. In our 2 year follow up study of patients with EB⁴ a progressive reduction in forced expiratory volume in 1 second of >20% was observed in three of the subjects, including a subject who developed asthma at the ninth month. We therefore plan to follow the disease course further in patients with EB.

Recent evidence suggests that the differences in functional association are related to differences in the localisation of mast cells in the airway wall, with airway smooth muscle infiltration occurring in asthma and epithelial infiltration in EB.⁵ Interaction between airway microcirculation and vascular endothelial growth factor (VEGF) may be a key element in the differences in airway function between asthma and EB.

Further study of the long term course of EB will increase our understanding of airway inflammation, airway responsiveness and airway remodelling to enable us to discriminate between EB and asthma.

A-S Jang, S-W Park, C-S Park

Asthma and Allergy Research Group, Division of Allergy and Respiratory Diseases, Soonchunhyang University Hospital, Korea

Correspondence to: Dr C-S Park, Division of Allergy and Respiratory Diseases, Department of Internal Medicine, Soonchunhyang University Bucheon Hospital, 1174, Jung Dong, Wonmi Gu, Bucheon Gyeonggi-do 420-021, Republic of Korea; mdcspar@unitel.co.kr

Competing interests: none declared.

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Authors' reply

We are grateful to Dr Brightling for his interest in our recent paper¹ and for raising