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STATEMENT OF INTEREST
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Anti-elastin autoantibodies are not present in combined pulmonary fibrosis and emphysema

To the Editors:

Whereas tobacco smoking is a well-established risk factor for the development and progression of chronic obstructive pulmonary disease (COPD), the molecular basis for individual predisposition and disease progression remains largely unknown. Immunological processes and especially autoreactive immune processes have recently been implicated, with anti-elastin antibodies and a T-helper type-1 lymphocyte response identified in patients with COPD/emphysema [1]. Immune mechanisms are also implicated in interstitial lung disease and pulmonary fibrosis [2], and smoking-induced autoimmunity has been demonstrated in rheumatoid arthritis [3].

We explored whether an autoimmune process implicating anti-elastin autoantibodies and facilitated by tobacco smoking may take place in patients with combined pulmonary fibrosis and emphysema (CPFE), a distinct entity recently defined on the basis of characteristic features of chest imaging, pulmonary function and outcome [4].

Patients with CPFE, diagnosed within the previous 5 yrs using published criteria based on computed tomography of the chest [4], were studied. Patients with connective tissue disease at the time of diagnosis were excluded. Control patients were selected from within the same department of respiratory medicine and had various diagnoses: idiopathic

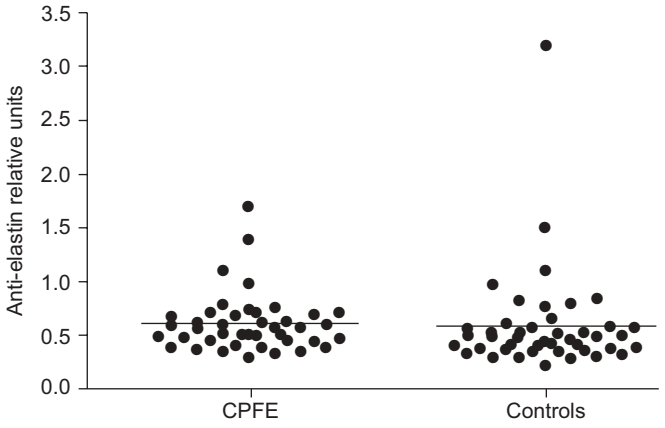

FIGURE 1. Quantification of anti-elastin antibodies using ELISA in patients with combined pulmonary fibrosis and emphysema (CPFE) and controls. Results >1 are considered positive. ——: median.

interstitial pneumonia (n=13); pre-capillary pulmonary hypertension (n=12); eosinophilic lung disease (n=7); sarcoidosis (n=2); Wegener's granulomatosis (n=2); and other diagnoses (n=6). Patient consent was obtained for the analysis of auto-immunity.

Anti-elastin antibodies were quantified using modified ELISA as previously described [1]. Microplates were coated with human lung elastin peptides (Elastin Products Company, Owensville, MO, USA) or with PBS (control wells) overnight, then washed and blocked. After washing, diluted human serum samples were incubated for 2 h, then washed, incubated with peroxidase-conjugated goat anti-human immunoglobulin G and revealed with *O*-phenylenediamine dihydrochloride. Optical density (OD) was determined at 490/620 nm. The specific binding of antibodies was evaluated by calculating the difference between the average OD of antigen-coated wells and that of control wells (using $2 \times$ SD above the mean of 100 sera from blood donors as a cut-off). A ratio (OD of sample/OD of cut-off value) above 1 arbitrary unit·mL^{-1} was considered positive.

We studied 42 patients with CPFE (37 males, five females), all smokers, with a mean age of 66.4 ± 10.2 yrs, and 42 controls (26 males, 16 females) with a mean age of 53.2 ± 22.8 yrs. Anti-elastin antibodies were detected in three out of 42 patients with CPFE, and three out of 44 control patients (who had Wegener's granulomatosis, Churg–Strauss syndrome and pulmonary hypertension, respectively; p=1.0, Fisher's exact test). The titre of anti-elastin antibody was not elevated in patients with CPFE compared with controls (0.61 ± 0.04 relative units *versus* 0.58 ± 0.07; p=0.74, unpaired t-test; fig. 1).

According to the model of LEE *et al.* [1], exposure to tobacco smoking might increase secretion of proteolytic enzymes in the lung from cells of the innate immune system, thereby liberating lung elastin fragments and initiating elastin-targeted T- and B-cell mediated immunity in susceptible individuals. Our results do not support the idea that either emphysema or fibrosis in CPFE may be mediated by an autoimmune process directed against elastin. Since all patients with CPFE had emphysema on imaging (mostly paraseptal emphysema, and also centrolobular emphysema), our results also fail to confirm the presence of circulating anti-elastin antibodies in patients with emphysema (at least when associated with fibrosis).

Future studies in CPFE will explore putative alternative immune processes described in other conditions. For instance, experimental autoimmune emphysema in mice may be caused by the development of antibodies against endothelial cells [5] or against vascular endothelial growth factor (VEGF) receptors [6], VEGF being a cytokine also implicated in lung fibrogenesis [7]. Autoantibodies against pulmonary epithelial cells have been reported in COPD [8], and might conceivably contribute to alveolar epithelial cell injury and activation and, furthermore, to pulmonary fibrosis, a process similar to abnormal wound repair [9].

Further work is needed to address the intriguing coexistence of pulmonary fibrosis and emphysema within the lung, two processes with distinct, if not opposite, pathogenesis.

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STATEMENT OF INTEREST

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Pre-immigration screening for pulmonary tuberculosis: the unanswered questions

To the Editors:

In a recent issue of the *European Respiratory Journal*, the article by MOR *et al.* [1] captured my interest. The results are no doubt promising but there are some points of concern that need to be highlighted.

Firstly, in a country such as Ethiopia, where there is a very high incidence of pulmonary tuberculosis (PTB), screening for latent tuberculosis infection (LTBI) by tuberculin skin test (TST) is not justified. This is because such a strategy has many limitations. The main problem is that of the sensitivity and specificity of TST. In immunocompromised persons, particularly those with HIV infection, the sensitivity is markedly reduced and the possibility of missing the diagnosis of tuberculosis is always there [2]. In addition, there is the problem of false-positive reactions as infections with non-tuberculous mycobacteria are highly prevalent in countries where tuberculosis is common [3]. Bacille Calmette-Guérin (BCG) vaccination is usually routinely given in newborns and schoolchildren in such countries and this may again lead to false-positive tuberculin reactions. Nearly one-third to one-half of all positive TST results among immigrants from countries with high and intermediate rates of tuberculosis are due to BCG vaccination [4, 5] and nontuberculous mycobacteria [4, 6].

In such circumstances, early detection and prompt treatment of active PTB cases is more justifiable than screening for LTBI.

Secondly, the reliability of chest radiography, used as a tool for screening in the study of MOR *et al.* [1] is still questionable. Persons with normal chest radiography may have active PTB [7], and even persons with chest radiography showing shadows suggestive of PTB may in reality not have active tuberculosis. Moreover, other factors such as poor quality of the chest radiograph and wide inter-observer variations [8] in the interpretation of chest radiographs may lead to misdiagnosis. False-negative diagnoses may pose a threat to public health through the spread of tuberculosis, whereas false-positive diagnoses will result in inefficient use of resources. Misdiagnosis of active tuberculosis as latent infection and subsequent use of single-drug chemoprophylaxis may result in drug resistance. As well, there is also the radiation hazard involved in performing chest radiography on all the immigrants. It is well known that radiation generates highly reactive free radicals and is carcinogenic, teratogenic and mutagenic. It has been associated with cancers of the thyroid, bone, lung, breast and leukocytes [9]. Like lead and asbestos, radiation has no safe threshold. Therefore, it would be wise to avoid all unwarranted exposure to ionising radiation, no matter how little it may be. So performing chest radiography in only those persons who have symptoms suggestive of PTB seems to be a more pragmatic approach, rather than using it as a screening method in a resource-constrained country such as Ethiopia.

Finally, the point that needs to be highlighted here is that the test for HIV should have been done in all immigrants in Ethiopia itself, not after reaching Israel. It is well known that HIV-infected persons usually have atypical presentations of PTB, both clinically as well as radiologically, and that these persons are less likely to be sputum smear-positive [10], though they may be harbouring active tuberculosis. TST in these persons is considered as positive even if the induration is $\geqslant$5 mm. Therefore, HIV testing for all persons before they reached Israel would have helped in better assessment of LTBI and to decide who the real candidates for chemoprophylaxis were and which were to get active treatment with antituberculosis drugs.

In a country with a high incidence of pulmonary tuberculosis, the prevalence of isoniazid resistance is also expected to be high. Thus, administration of a single drug for chemoprophylaxis should be done more judiciously, especially when the epidemic of multi-drug resistant tuberculosis is at its peak and the threat of extensively drug resistant tuberculosis is hovering over us.

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STATEMENT OF INTEREST

None declared.

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