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Title: Immune activation in α 1 antitrypsin deficiency (AATD) emphysema: Beyond the protease/antiprotease hypothesis

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Body: The protease/antiprotease hypothesis has long set the field in the pathogenesis of AATD related emphysema, while activation of lymphocyte-driven responses has been scarcely investigated in this condition. We performed this study to evaluate the involvement of adaptive immune responses in AATD patients. By immunohistochemistry and molecular analysis we evaluated number, topographical distribution and clonality of lymphoid follicles in native lungs of AATD patients undergoing transplantation for severe emphysema (n=10). Results were compared to patients with similar disease severity, but with normal AAT levels (n=26) and to smoking (n=17) and nonsmoking (n=12) controls. Lymphoid follicles (LF) were significantly increased in the lungs of emphysematous patients, either with AATD (4.1;0.7-13 LF/cm²) or without AATD (1.5;0-5.1) as compared to smoking (0;0-5) and nonsmoking controls (0;0-1, all p<0.05). Somewhat surprisingly the number of LF was even more prominent in patients with AATD than in those with normal AAT levels (p<0.05). Follicles in patients with AATD were predominantly located in the lower lobe, where lung destruction predominates. Molecular analysis confirmed an oligoclonal response in B cells isolated from these follicles. In conclusion, our study shows that organization of lymphocytes in follicles is a prominent feature of subjects with severe emphysema and AATD. These results challenge the current paradigm of α 1 antitrypsin deficiency-related emphysema from a protease/antiprotease driven process only to a more complex scenario entailing activation of adaptive immune responses. Funded by Padua University, CARIPARO, Chiesi farmaceutici.