Title: Severe lung inflammation is a feature of IPF

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Body: Background. Lung inflammation is neither considered an important feature of IPF nor an important factor in its pathogenesis. However the degree and type of lung inflammation has never been carefully quantified and characterized in the different phenotypes of IPF. Aim. To quantify and define the type of inflammation in slow decliners (S), rapid decliners (R) and acute exacerbation (AE) phenotypes of IPF and relate it to the functional decline. Methods. 59 patients IPF, referred for lung transplant, were followed for 37 (12-156) months. A 10% FVC decline/year cut-off was used to define the R (>10%) and S (<10%) phenotypes. 27 explanted lungs were available for the study. Lung inflammation was quantified in sections from upper and lower lobes that were immunostained for total leukocytes (CD45), neutrophils, macrophages, CD4 and CD8 T-cells. Results. Total leukocytes were markedly increased in R (median; range: 653;428-973 cells/mm²) and AE (682;513-921 cells/mm²) when compared with S (213;91-252 cells/mm²) (p<0.001 for both). Neutrophils, macrophages and T lymphocytes were significantly higher in R and AE when compared to S (p<0.05 for all). Severe inflammation was observed in normal, intermediate and honeycombing areas in R, intermediate and honeycomb areas in AE and in no areas in S. Total leukocytes correlated with the yearly decay in FVC (r=0.8; p=0.002). Conclusions. A severe innate and adaptive inflammation differentiates the S from the R and AE phenotypes of IPF. The apparent correlation between inflammation and decline suggests a possible role for inflammation on the mechanism of rapid progression in IPF. Different phenotypes should be taken in consideration in the design of treatment trials.