# Extraarticular manifestations of Rheumatoid Arthritis: Focus on lung disease

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The systemic manifestations of rheumatoid arthritis (RA) are common but often underappreciated for their significant impact on morbidity and premature mortality in this disease. The cumulative incidence of extraarticular disease (ExRA) including vasculitis, pulmonary disease, nodulosis, scleritis and other manifestations is 46%. ExRA is associated with a doubling of the already 2-fold risk of cardiovascular disease, and markedly increased risk for premature death compared to patients with RA who do not have ExRA. Clinical predictors of ExRA include a positive antinuclear antibody, male gender, positive rheumatoid factor, HLA-C, and HLADR0401 and 0404. Smoking is associated with a 2-fold increase in the risk for developing RA, and among patients with RA further doubles the risk of ExRA. Lung involvement occurs in 10-50% of patients with RA. The lung disease is diverse, and includes several forms of interstitial pneumonitis (IP), as well as bronchiolitis obliterans and upper airway disease. Histopathologic evaluation of lung tissue from patients with RA-associated IP reveals increased populations of CD4, CD8 and CD20 cells regardless of the histologic subtype. Citrullinated peptides are found in the lungs of patients with IP, especially in association with RA related IP, likely resultant from chronic inflammation. Populations of $CD56^{+}$ cells are increased in patients with EXRA. These chronically activated T cell receptors are fully competent, as evidenced by the widespread tyrosine phosphorylation they induce and by their avid stimulation of cytokine production, including macrophage inhibitory protein, interleukin-2 and tumor necrosis factor $\alpha$. There are no controlled studies of treatment of ExRA. Management emphasizes control of the underlying disease. Glucocorticosteroids are the mainstay of treatment, supplemented in severe disease by cytotoxic and anticytokine therapies.