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Editorial

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Advocating for early interstitial lung disease detection in mixed connective tissue disease

ILD detection in mixed connective tissue disease

With the advent and widespread availability of thoracic high-resolution CT (HRCT) scanning, an increased awareness of the high prevalence of interstitial lung disease (ILD) in CTD has been acknowledged. It is now recognized that ILD is identified in the majority of patients with scleroderma and frequently identified in those with idiopathic inflammatory myopathy and RA as well [1, 2]. The presence of ILD in these disorders is associated with a significant increase in morbidity and shortened survival rates [3]. Curiously, chronic ILD is rarely encountered in those with SLE, typically occurring in $<5\%$ of cases [4]. Far less is known about the prevalence or impact of ILD in those with mixed CTD (MCTD). In this issue of *Rheumatology*, Reiseter *et al.* [5] provide an important contribution to our understanding of the prevalence, natural history and impact of ILD in patients with MCTD.

The cohort studied by Reiseter *et al.* is one of the first to provide a reliable estimate of the prevalence of ILD in MCTD. In this study population, the prevalence of ILD as determined by HRCT was 40%. The cohort reflected the unselected nationwide Norwegian MCTD population with serial CT and pulmonary function testing, although it is less clear whether there was a bias towards inclusion of patients with respiratory symptoms that prompted an initial CT scan. Nonetheless, this study suggests that there is a high prevalence of ILD in MCTD.

The finding of ILD via HRCT was not a trivial radiologic abnormality. Over time, radiographic progression was noted in nearly half of those with ILD at baseline. Progressive patients were more likely to be male, have higher titre anti-RNP antibody and have worse lung function at baseline. Furthermore, as compared with those without ILD on baseline HRCT, those with ILD had significantly lower 5- and 10-year survival. The cumulative survival rates are quite striking: among those with at least 5% of total lung volume (TLV) involved on HRCT, 10-year survival was 70% as compared with 87% for those without ILD or with ILD involving $<5\%$ of TLV ($P = 0.015$). And for those with $>10\%$ of TLV, the 10-year survival fell to 60%. Taken together, this study affirms that the finding of ILD in MCTD is common, impacts survival and underscores the prognostic importance of disease extent as measured by HRCT.

ILD in the setting of MCTD is likely an underrecognized problem. We suspect it is more common than previously known and impacts the overall survival of MCTD when present. Currently assessment for ILD in MCTD is left to individual practitioners, as there are no guidelines for ILD screening in this population. Given the impact that small changes in HRCT disease extent have on mortality, early identification and diagnosis is paramount. Plain chest X-ray will not detect mild disease, and waiting for symptoms to develop or for a decline in lung function may be too late. We believe that the findings in this study should prompt consideration of integrating screening HRCT for early detection of ILD among those with MCTD, even in the absence of symptoms. We recommend patients undergo thoracic HRCT imaging and full pulmonary function testing (spirometry, lung volume and diffusing capacity) when a diagnosis of MCTD is confirmed in order to detect whether ILD is present and to establish baseline lung function. In the absence of ILD, we recommend annual spirometry with diffusing capacity to screen for changes in lung function that may suggest the development of ILD or pulmonary vascular disease. If ILD is detected, referral to a pulmonologist and/or a dedicated ILD centre is encouraged.

Identifying ILD is an important first step. Such detection ideally provides the opportunity for early therapeutic intervention, particularly in patients that demonstrate disease progression by imaging or pulmonary physiology. It is plausible to believe that targeted intervention with immunomodulatory therapies will slow progression and favourably impact the survival of MCTD patients with ILD.

In the Scleroderma Lung Study [6], patients with scleroderma-associated ILD treated with CYC demonstrated a modest improvement in lung function, quantitative CT imaging and dyspnoea and quality of life measures. The Scleroderma Lung Study II [7] provided further evidence that CYC is effective for scleroderma-ILD and demonstrated a similar effect with MMF, which was better tolerated and caused fewer adverse effects. Retrospective data similarly suggest that MMF is a well-tolerated long-term treatment option across a broad spectrum of CTD-ILD and is associated with improved lung function and corticosteroid-sparing effects [8]. Beyond these two agents, AZA, ciclosporin, tacrolimus and rituximab all show some degree of efficacy in CTD-ILD in general. Although not studied specifically in MCTD-ILD, immunosuppression likely has some degree of efficacy, and a strategy of early intervention would seem logically preferred over late intervention.

The study by Reiseter *et al.* [5] is a significant step forward. It adds to what is known about the prevalence, disease course and impact of ILD in MCTD. This knowledge provides an opportunity to be proactive in the care of our patients with MCTD and implement early screening and evaluation for the presence of ILD. It may also provide an opportunity for early intervention with well-tolerated and safe immunosuppressive medications for those with progressive disease and ultimately help in our goal of improving and prolonging patients' lives.

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References

1 Fathi M, Lundberg IE. Interstitial lung disease in polymyositis and dermatomyositis. Curr Opin Rheumatol 2005;17:701–6.

2 Castelino FV, Varga J. Interstitial lung disease in connective tissue diseases: evolving concepts of pathogenesis and management. Arthritis Res Ther 2010;12:213.

3 Park JH, Kim DS, Park IN *et al*. Prognosis of fibrotic interstitial pneumonia: idiopathic versus collagen vascular disease-related subtypes. Am J Respir Crit Care Med 2007;175:705–11.

4 Weinrib L, Sharma OP, Quismorio FP. Jr. A long-term study of interstitial lung disease in systemic lupus erythematosus. Semin Arthritis Rheum 1990;20:48–56.

5 Reiseter S, Gunnarsson R, Aalokken TM *et al*. Progression and mortality of interstitial lung disease in mixed connective tissue disease: a long-term observational nationwide cohort study. Rheumatology 2017. doi: 10.1093/rheumatology/kex077. [Epub ahead of print].

6 Tashkin DP, Elashoff R, Clements PJ *et al*. Cyclophosphamide versus placebo in scleroderma lung disease. N Engl J Med 2006;354:2655–66.

7 Tashkin DP, Roth MD, Clements PJ *et al*. Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. Lancet Respir Med 2016;4:708–19.

8 Fischer A, Krishnamoorthy M, Olson AL *et al*. Mycophenolate mofetil (MMF) in various interstitial lung diseases. Am J Respir Crit Care Med 2012;185:A3638.