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Authors' Reply to Diagnostic Pitfalls and Treatment Challenges in Interstitial Pneumonia with Autoimmune Features

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We thank Dr. Novikov and colleagues for their thoughtful comments on our recent review [1]. We agree that the ATS/ERS classification criteria for IPAF [2] will most certainly need to be reviewed, revised, and validated moving forward. We also agree whole-heartedly with the critical collaboration between rheumatologists and pulmonologists in the management of these patients. In our ongoing prospective longitudinal cohort, >93% of patients are co-managed by rheumatology and pulmonology. We strongly advocate this approach worldwide both to provide accurate classification/diagnosis at the time of presentation and to monitor for the emergence of a clearly defined connective tissue disease (CTD).

We agree that ANCA testing should occur in the setting of new interstitial lung disease (ILD), although ANCA testing was not universally recommended in the 2018 idiopathic pulmonary fibrosis diagnostic guidelines [3]. Whether or not a patient with ILD and positive ANCA is undifferentiated, however, is much less clear. In 2014, Saadoun and coworkers conducted a retrospective review of patients with pulmonary fibrosis and ANCA-associated vasculitis (AAV), with myeloperoxidase antibody specificity being far more common than proteinase-3 specificity. They reported that approximately 40% of patients had evidence of pulmonary fibrosis ahead of clinically apparent vasculitis, and another 40% presented with both pulmonary fibrosis and evidence of systemic vasculitis, usually microscopic polyangiitis. A variety of radiographic patterns were present. Interestingly, patients with pulmonary fibrosis had a poor prognosis with a global mortality of 56%, which was somewhat improved by induction therapy consisting of glucocorticoids plus either cyclophosphamide or rituximab versus glucocorticoids alone [4]. The induction treatment regimens for AAV differ from initial treatment of other CTD-ILDs, so these patients would likely benefit from targeted vasculitis therapy. Additionally, draft ACR/EULAR

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classification criteria for AAV would classify these patients as having AAV [5], which would exclude them from the IPAF algorithm should those criteria be ultimately ratified.

We also agree that there is significant ambiguity in treatment algorithms. In refractory disease, it is reasonable to try a variety of immunosuppressive agents, and there may not be a clear order in which to trial various therapies. We agree with using a personalized approach depending on the exact clinical picture and patient preferences. We do think that calcineurin inhibitors are an emerging therapy for myositis related ILD as highlighted in other recent reviews [6, 7], and there is previously documented efficacy in rheumatoid arthritis [8]. Admittedly, it may be less ideal in systemic sclerosis given the risk of renal adverse events. Additionally, for patients with severe interstitial lung disease for whom lung transplantation may be necessary, some transplant centers may have considerable reluctance to transplant after administration of either cyclophosphamide or rituximab. As calcineurin inhibitors are used routinely post-transplant, these medications may be viewed differently by some transplant pulmonologists and preserve transplant candidacy.

In summary, we welcome the ongoing discussion about these criteria, diagnostic approaches, and management strategies. We feel that patients with ANCA associated ILD likely have AAV rather than an IPAF based on the most recent draft ANCA vasculitis criteria. We also welcome ongoing collaborations and multicenter cohorts to truly validate these criteria and determine the best treatment options.

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