Guillermo Suarez-Cuartin[1,2], Maria Molina-Molina[1,2]

gsuarezc@bellvitgehospital.cat

es.linkedin.com/in/guillermo-suarez-cuartin-947224181

Journal club

Clinical implications of ANCA positivity in idiopathic pulmonary fibrosis patients

Commentary on:

Liu GY, *et al*. Prevalence and clinical significance of antineutrophil cytoplasmic antibodies in North American patients with idiopathic pulmonary fibrosis. *Chest* 2019; 156: 715–723.

Context

The diagnostic process of idiopathic interstitial pneumonias (IIPs) is complex and the underlying mechanisms that participate in these diseases still need to be fully understood. In 2015, the European Respiratory Society/American Thoracic Society Task Force on Undifferentiated Forms of Connective Tissue Disease-Associated Interstitial Lung Disease introduced the term "interstitial pneumonia with autoimmune features" (IPAF) to identify subjects with IIP and features suggesting background autoimmunity but not characterisable connective tissue disease (CTD) [1]. The need for a proper clinical, serological and morphological assessment of IIP was highlighted to identify potential subjects with IPAF and CTD-ILD. However, the measurement of anti-neutrophil cytoplasmic antibodies (ANCAs) is not included in the definition of IPAF and ANCA serological testing is only recommended in idiopathic pulmonary fibrosis (IPF) when a clinical suspicion of vasculitis exists [2]. As current research evaluates the prognostic relevance of autoimmune features in IIP, the clinical importance of ANCA positivity still needs to be determined.

The most frequently identified ANCAs are myeloperoxidase (MPO) and proteinase 3 (PR3) antibodies, and both are usually associated with systemic vasculitis such as microscopic polyangiitis (MPA) [3]. These autoantibodies are found in up to 10% of patients with IPF at the moment of diagnosis, with no clinical manifestations of systemic vasculitis [4–6]. Furthermore, ~10% of ANCA-negative IPF patients seroconvert during follow-up [4–6] and up to 26% of MPO-ANCA-positive patients develop MPA. Regardless of this prevalence, serological testing for ANCAs is not usually included in the systematic assessment for IIP or IPAF [1, 2, 7]. Nevertheless, the prevalence and clinical implications of ANCAs in North American patients is not well known, since most of the aforementioned studies are from Japanese populations. In this regard, Liu *et al.* [8] retrospectively studied two independent North American IPF cohorts to better understand the prevalence of ANCA positivity at the moment of diagnosis and determine its clinical relevance.

Methods

This retrospective study evaluated two cohorts of IPF patients enrolled prospectively in longitudinal

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ANCA positivity is uncommon in North American IPF patients. However, women with IPF who are MPO-positive have a considerable risk for developing clinical manifestations of vasculitis.
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registries and biorepositories from the University of California San Francisco (UCSF) (discovery cohort) and the University of Chicago (UC) (replication cohort). Study participants were required to have been diagnosed with IPF by an in-person multidisciplinary discussion supported by clinical guidelines. Study subjects were also required to have either stored serum obtained at diagnosis or ANCA testing during the diagnostic evaluation. Clinical, radiological, serological and histopathological data were collected at enrolment. MPO and PR3 ANCAs were measured from stored serum samples in all UCSF patients and as a part of the diagnostic evaluation in all UC patients. For all patients in the discovery cohort, a standardised evaluation including semiquantitative scores for individual features was performed on all chest computed tomography (CT) scans and available surgical lung biopsy samples, blinded to ANCA status. However, standardised CT scans and pathology scores were not available for the replication cohort. Patients were categorised as ANCA positive or ANCA negative for either MPO or PR3 antibodies for clinical and radiological comparison, and survival time analysis was performed both unadjusted and adjusted for age, sex and lung function test percentage of predicted values.

Main results

The discovery cohort included 353 patients, 14 of whom were ANCA positive at the time of enrolment (4.0%, 95% CI 2.2–6.5%). Of these patients with ANCAs, six (43%) out of 14 had MPO antibodies and eight (57%) out of 14 had PR3 antibodies. The proportion of ANCA detection was similar in the replication cohort including 392 patients, amongst whom 20 (5.1%, 95% CI 3.1–7.8%) were ANCA positive. 12 subjects (60%) had MPO antibodies, two (10%) had PR3 antibodies and six (30%) had nonspecific ANCA positivity. In both cohorts, ANCA positivity predominated in women (discovery cohort: 47.1% *versus* 22.9%, p=0.09; replication cohort: 50.0% *versus* 25.0%, p=0.01) but no significant differences were found regarding age or pulmonary function tests. In the discovery cohort, six (75%) out of eight of PR3-positive patients and two (33.3%) out of six MPO-positive patients were male. This sex distribution was similar in the replication cohort, where seven (87.5%) out of eight PR3-positive or nonspecific ANCA-positive patients and four (33.3%) out of 12 MPO-positive patients were male. Other antibodies, such as rheumatoid factor and anti-nuclear antibodies, were detected in six (42.9%) out of 14 of the discovery cohort and 20 (100%) out of 20 of the replication cohort.

After analysing radiological features of the discovery cohort, significant differences were found between ANCA-positive and ANCA-negative patients regarding the presence of ground-glass opacities on the chest CT scan (33.3% *versus* 9.3%, respectively; p=0.02), and detection of moderate or severe honeycombing (33.3% *versus* 10.5%, respectively; p=0.04). There were no significant differences in usual interstitial pneumonia (UIP) classification, distribution of fibrosis, consolidation, nodules or other specific features. CT scans were not available for analysis from the replication cohort. Due to the limited number of pathology samples available, no statistical comparison was performed. Although no evidence of capillaritis or vasculitis was observed in any of them, histological findings in lung biopsy samples from ANCA-positive patients included varied patterns other than UIP, such as nonspecific interstitial pneumonia and organising pneumonia.

Median follow-up time was 18.3 and 10.5 months for the discovery and replication cohorts, respectively. During follow-up, two (33%) of the MPO-positive patients in the discovery cohort developed a clinical diagnosis of MPA and three (25%) of the patients with MPO antibodies in the replication cohort also developed clinical vasculitis (one case of MPA and two of nonspecific ANCA-associated vasculitis). All subjects with clinical vasculitis were women and MPO positive in both cohorts. Predominant clinical manifestations were renal disease (60%) and mononeuritis multiplex (40%). Median transplant-free survival time showed no significant difference for the combined cohort (ANCA positive: 5.0 years, 95% CI 3.8–∞ years; ANCA negative: 4.9 years, 95% CI 3.8–5.6 years; log-rank p=0.57). No significant difference in survival was found after controlling for age, sex and pulmonary function tests.

Commentary

One of the main results of this study is that a limited number of North American IPF patients are ANCA positive (MPO and PR3) at the time of diagnosis but one in four patients with positive MPO antibodies will develop clinical features of vasculitis during follow-up. The investigators also observed that the prevalence of ANCA positivity appears to be higher in IPF patients compared to the general population; nevertheless, it is slightly lower than that described for the Japanese IPF population for the MPO antibodies [4, 6, 9] and similar for the PR3 antibodies [5, 6]. However, since this study did not evaluate consecutive ANCA measurements, potential seroconversion during follow-up was not assessed. No underlying mechanisms have been associated between ANCA antibodies and IPF but this study could suggest that a minority of IPF patients might develop clinical vasculitis or, conversely, that some patients with vasculitis with only pulmonary fibrotic manifestation may initially mimic IPF. Therefore, ANCA testing should be considered in some cases.

No clinical differences between ANCA-negative and ANCA-positive subjects were identified, except for patient sex. Previous studies have shown an

equal sex distribution or male predominance in ANCA-positive patients [4, 5, 9, 10]. However, in this study, a clear predominance of women was observed in MPO-positive subjects, while all PR3-positive individuals were male. These findings highlight the differences amongst ANCA-positive IPF populations from North American cohorts and those from previous studies, which may limit the generalisability of the results.

There are controversial findings regarding radiological differences on the chest CT scans of ANCA-positive and ANCA-negative IPF subjects. Liu *et al.* [8] observed that patients with ANCA positivity show a significantly higher prevalence of ground-glass opacities. Another study by Hosoda *et al*. [9] identified similar results and found a higher inflammatory cell infiltration in the lung biopsies of MPO-positive IPF patients. Although the small number of lung biopsies was a limitation to analysing potential differences, the radiological findings could also translate into a predominant lung inflammation of the ANCA-positive IPF subjects.

The development of clinical vasculitis (MPA) during follow-up among IPF patients who were MPO positive was 25%–33%, similar to that observed in other IPF populations [6, 9]. In this study, all the patients who developed MPA were women and MPO positive. Like other serological autoantibodies in systemic diseases that may be positive without an initial extrapulmonary involvement, MPO positivity in the clinical context of pulmonary fibrosis could be considered a serological domain of IPAF [11, 12].

The most frequent extrapulmonary manifestations of MPA in this study were renal impairment and mononeuritis multiplex, as observed in previous reports [6, 10, 13]. Interestingly, no signs of vasculitis were found in any of the available lung biopsies at baseline. Thus, regardless of the presence of extrapulmonary manifestations of vasculitis in MPO-positive patients, pulmonary involvement may appear in the form of UIP or other forms of pulmonary fibrosis. MPA may, therefore, be underrecognised among IIP cases.

Finally, this study did not find a significant difference in terms of survival time between ANCA-positive and ANCA-negative IPF patients. MPA patients with ILD present higher mortality than those without associated ILD [14] but no data exist regarding the impact of ANCA positivity in IIP. Prospective long-term studies would be required to evaluate whether ANCA-positive IPF patients present different outcomes, or even if MPO and PR3 positivity could differently impact on clinical behaviour and survival.

This is the first and largest study to assess the prevalence of ANCA positivity in North American IPF patients with a systematic approach and using two different populations, observing comparable results. Nevertheless, ANCA testing was only performed at baseline and the follow-up period was limited, potentially underestimating the risk of developing clinical vasculitis. In addition, the small number of ANCA-positive IPF cases is a challenge to find specific radiological or pathological features. Therefore, multicentre longitudinal studies including a larger number of IPF patients would be required to evaluate whether MPO and PR3 positivity may be associated with specific clinical features and different outcomes.

Implications for practice

This study shows that female IPF patients who are MPO positive have a 25–33% risk of developing clinical vasculitis. Although these results do not support routine measurement of ANCAs (PR3 and MPO) in all IPF patients, MPO positivity could be considered an immunological feature and an IPAF criterion in the future. Clinicians should be aware that testing for MPO antibodies may be considered in women with IPF due to the clinical and therapeutic implications of developing vasculitis.

Affiliations

Guillermo Suarez-Cuartin[1,2], Maria Molina-Molina[1,2]

[1]Hospital Universitari de Bellvitge, L'Hospitalet de LLobregat, Barcelona, Spain. [2]Institut d'Investigació Biomèdica de Bellvitge, L'Hospitalet de LLobregat, Barcelona, Spain. .

Conflict of interest

G. Suarez-Cuartin has nothing to disclose. M. Molina-Molina reports grants from Boehringer Ingelheim, Roche, GlaxoSmithKline, Esteve-Teijin, Almirall and Chiesi, outside the submitted work.

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