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The role of serological testing in idiopathic interstitial pneumonia: a rheumatologist perspective

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Abstract The diagnosis of idiopathic interstitial pneumonias (IIPs) is complex and requires multidisciplinary approach. Identifying an underlying connective tissue disease (CTD) is associated with a better prognosis and should be routinely evaluated. Serological testing is an important tool in detecting patients with CTDs and differentiating them from patients with IIP. This article will highlight the importance of serological testing in patients with IIPs and the role of the rheumatologist in evaluating these patients.

Keywords Idiopathic interstitial pneumonias · Connective tissue diseases · Autoantibodies · Lung dominant connective tissue disease

Introduction

Idiopathic interstitial pneumonias (IIPs) are a group of interstitial lung diseases with no known etiology. There are several entities with varying patterns of inflammation and fibrosis. In 2002, the American Thoracic Society (ATS) and the European Respiratory Society (ERS) have developed an international multidisciplinary classification of the IIPs [1]. This statement was recently updated in 2013 [2]. One important addition in the classification of IIPs is the acceptance of nonspecific interstitial pneumonia (NSIP) as a clinic-pathological entity [3], which is more commonly associated with underlying connective tissue disease (CTD) [4]. It has been observed that CTD-related interstitial lung disease (CTD-ILD) carries a better prognosis than the IIPs [5, 6]. Autoantibody testing is recommended to evaluate patients with symptoms suggestive of CTD such as joint pain, oral ulcers, skin rash, and many others [7]. Pulmonary involvement is variable in CTDs [8••]. Currently; there are no strong data to confidently recommend serological testing in patients with IIPs. Despite the lack of evidence, the ATS, ERS, the Japanese Respiratory Society (JRS), and the Latin American Thoracic Association (ALAT) have conjointly recommended that serologic testing for CTDs should be performed in the evaluation of the majority of patients with idiopathic pulmonary fibrosis [9]. The antinuclear antibody (ANA) and rheumatoid factor (RF) are the most commonly used autoantibodies for screening of patients with suspected CTDs. They are found in the normal population [10, 11] as well as in a variety of non-rheumatic causes [12] including idiopathic pulmonary fibrosis [13•].

Routine evaluation might sometime not be adequate to identify the underlying CTD which would wrongly lead to labeling a patient as having IIP. Solutions to this problem would include the use of nailfold capillaroscopy [14•], extensive serological testing [15], and minor salivary gland biopsy [16]. In this report, we will discuss why would an extensive serological testing might lead to identify more patients with underlying CTDs and the role of the rheumatologist in identifying it.

The advances in autoantibody detection in patients with CTDs

Antibodies to specific antigens have been discovered in the last three decades that proved to be important in the diagnosis and management of CTDs. They are useful in screening and

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predicting disease subset, complications, and even survival. Many of these autoantibodies were detected in the sera of patients before the onset of symptoms [17–20]. The idiopathic inflammatory myopathies (IIMs) include dermatomyositis (DM) and polymyositis (PM). Autoantibodies against the cytoplasmic aminoacyl-tRNA synthetase (ARS) enzymes are the most frequently detected in patients with IIMs [21]. The classical and most widely tested is the Jo-1 (histidyl tRNA-synthetase) [22] which is only found in 20 % of patients [23, 24]. To date, seven other anti-ARS molecules have been identified and are collectively found in 20 % of IIM patients which includes PL-7 (threonyl) [25], PL-12 (alanyl) [26], EJ (glycyl) [27], OJ (isoleucyl) [28], KS (asparaginyl) [29], Ha (tyrosyl) [30], and most recently Zo (phenylalanyl) [31]. Most of these new antibodies were detected in the anti-synthetase syndrome which commonly includes interstitial pneumonia and might be the predominant feature [32–34]. In a series of 34 patients with clinically proven anti-synthetase syndrome with lung involvement, 9 (24 %) of them were ANA and Jo-1 negative but positive for PL-7 and PL-12 [35]. The anti-CADM-140 is a non-ARS antibody which is usually associated with cutaneous manifestations and minimal muscle involvement that can be complicated by a rapidly progressive interstitial pneumonia especially in the Asian ethnicity [36, 37]. Ye et al. reported the 6 months survival of patients with predominant ILD with a positive anti-CADM-140 antibody to be 40.8 % [38]. Other rare autoantibodies include the anti-SRP, anti-Mi-2, and anti-p155/140, all have been also demonstrated to be present in IIMs but do not have a clear association with lung disease [39].

Similarly, in the field of systemic sclerosis (SSc), the two classical autoantibodies frequently used are topoisomerase I antibody which has been linked to the diffuse subset and lung involvement [40–42] and anti-centromere [43] which is usually found in the limited subset and predicts pulmonary hypertension. The estimated frequencies at its best of topoisomerase I and anti-centromere in the SSc population are 15–20 % and 20–30 %, respectively [44]. While other autoantibodies such as RNA polymerase III [45, 46], Th/To [47], and PM-Scl [48] which can be detected in patients tested negative for the former two antibodies can be of significant importance and predict progression and lung involvement [49, 50] are not commonly used in daily clinical practice. In one study of patients with a clinical diagnosis of IPF and surgical lung biopsy-proven usual interstitial pneumonia (UIP), the presence of a nucleolar ANA pattern and anti-Th/To was associated with the presence of many symptoms suggestive of SSc sine scleroderma (ssSSc) and limited SSc that most did not meet the classification criteria [51]. Interestingly, the prognosis in Th/To positive and Th/To negative patients was similar. This finding was similarly demonstrated from our center where the presence of autoantibodies in patients with IPF was not associated with an improved survival [hazard ratio (HR) 0.68, 95 % CI 0.202–2.347; P=0.550], rather the presence of autoimmune symptoms conveyed a statistically significant improved survival (HR 0.27; 95 % CI 0.09–0.82; P=0.020) [13•]. This finding could make us believe that the presence of autoantibodies by themselves does not improve survival, but their role is by improving the detection of underlying CTD.

Limitations of current classification criteria

Initial classification criteria published for CTDs have been designed from the 1980s forward and primarily used to include patients into clinical trials, cohorts, and registries. Many of these criteria have undergone extensive revisions because of the following limitations. First, they were developed from patients with established diseases leading to inclusion of late specific components with a lower sensitivity. This issue has been solved by extraction of new criteria from a mixed population of early and late. Additionally, different methodologies have been innovated to develop more robust and clinically meaningful criteria. As an example, the 2010 American College of Rheumatology (ACR)—European League Against Rheumatism (EULAR) for RA [52] were developed by different methodologies compared to the 1987 ACR criteria [53]. Second, new investigational tools have been recognized as useful and feasible to be used for the diagnosis of CTDs. A clear example is the addition of nailfold capillaroscopy to the 2013 ACR-EULAR classification criteria for systemic sclerosis [54] compared to the preliminary 1988 criteria [55]. Third (as discussed above), the discovery and addition of new autoantibodies have helped to stratify more patients. Two important examples are RNA polymerase III to the 2013 ACR-EULAR classification criteria for SSc, and the addition of cyclic citrullinated peptide (CCP) antibodies to the 2010 ACR-EULAR classification criteria for RA. Finally, weight has been given to the autoantibody titer such as the 2010 ACR-EULAR classification criteria for RA (2 points for low positive RF or anti-CCP and 3 points for high positive RF or anti-CCP). As a result, the new criteria classified more patients to have the disease and deemed more sensitive [56, 57]. Despite of all of these measures, classification criteria are still not perfect and their application on patients presenting with predominant respiratory symptoms or findings suggestive of IIPs is still unknown.

Rare syndromes in CTDs with lack of predominant features

Some patients with CTDs lack the predominant feature of their primary disease which deviates clinicians from suspecting these conditions which might lead to a significant delay in diagnosis and subsequent organ failure [58, 59]. An important aspect in diagnosing these patients is the identification of the subtle clinical findings and the detection of specific autoantibodies. Two important syndromes are ssSSc and amyopathic DM (ADM). In 1986, Giordano et al. proposed

the term ssSSc as a distinct subtype of SSc with visceral involvement and no skin manifestations. It has been shown that these patients have similar visceral involvement to the limited subtype but has more respiratory symptoms [60]. ADM was associated with a poorer ILD survival in comparison with classic DM and PM [36] with a mortality reaching 67 % when complicated by acute/subacute ILD [37].

Lung dominant CTDs

The lung is a major target for CTDs. In the presence of an established CTD and lung manifestations, the causal relation is clear assuming that infectious causes and drug adverse events have been properly excluded. In some conditions, lung involvement precedes other symptoms. Homma et al. prospectively followed 68 patients with a diagnosis of IIPs at inclusion for a duration of 1–11 years. Thirteen (19 %) of them developed systemic manifestations of CTD adequate to label them as having CTD-related IIP [61]. In 2007, Kinder et al. have discussed the matter that idiopathic NSIP might be the lung manifestation of undifferentiated CTD (UCTD) and suggested that the occurrence of one prespecified symptom or signs of CTDs plus the presence of systemic inflammation (either autoantibody or acute phase reactant) would be highly suggestive of UCTD [62]. Later on, Fischer et al. have discussed the challenges and limitations of evaluating patients with IPs (not confined to one histological subtype) and findings suggestive of an underlying CTD that do not meet classification criteria of CTD. They have proposed the concept of lung-dominant CTDs (LD-CTD) and suggested provisional criteria [15]. The serological testing suggested in these criteria is much more extensive than that proposed by Kinder et al. [62].

Pereira et al. reported the prevalence and characteristics of patients fulfilling the LD-CTD criteria (proposed by Fischer et al.) in 1998 ILD patients. Fifty-two (2.6 %) fulfilled the criteria. After a median follow-up of 61 months, 8 (15.3 %) fulfilled the classification criteria of a specific CTD [63••]. Omote et al. reported the most common histological pattern of LD-CTD is the usual interstitial pneumonia (UIP) followed by NSIP. Patients with NSIP had a significant improvement in the annual change in percent predicted forced vital capacity and better survival compared to patients with UIP [64••].

The rheumatologist as part of the IIP multidisciplinary team

The multidisciplinary team evaluating patients with suspected IIPs consists of pulmonologists, radiologists, and pathologists [2]. The role of rheumatologists is still not fully explored. Many rheumatologists are not familiar with the concept of LD-CTD and might hesitate to accept it as a form of UCTD or as a specific disease subtype because of the exclusive presentation of lung pathology with the complete absence of extrathoracic CTD manifestations. As an example, if a 40-year-old lady is evaluated for respiratory symptoms, CT scan findings of NSIP and histological lung features include lymphoid aggregates with germinal centers, extensive pleuritis, prominent plasmacytic infiltration and dense perivascular collagen with the presence of a positive ANA and topoisomerase I antibody without any other clinical symptoms. The pulmonologist would be reluctant to label her as suffering from idiopathic NSIP; on the other hand, the rheumatologist has no adequate evidence to diagnose this patient as having SSc. This lack of consensus would lead to confusion and undesirable consequences affecting patient management and prognosis. Solutions to this problem are increasing the awareness of LD-CTD concept in the rheumatology society and incorporating the rheumatologist into the multidisciplinary team evaluating patients with suspected LD-CTD.

Conclusion

Routine evaluation of patients with IPs is not adequate and can lead to misclassification and mismanagement. The presence of autoantibodies in patients with IIPs would not improve prognosis in all subtypes, but a more extensive serological testing can lead to a better detection of underlying CTDs which might eventually offer better therapeutic option and have a more favorable prognosis. Increasing awareness of rheumatologists about the concept of LD-CTD and involving them in evaluation of these patients might lead to a better informed decision and patient care.

Compliance with Ethics Guidelines

Conflict of Interest The authors declare that they have no competing interests.

Human and Animal Rights and Informed Consent This article contains no studies with human or animal subjects performed by the author.

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