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The Autoimmune Side of Heart and Lung Diseases

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Abstract The elevated cardiovascular morbidity in rheumatoid arthritis, systemic lupus erythematosus, and the antiphospholipid syndrome is well known, as well as the pulmonary involvement observed in these conditions and to a major extent in systemic sclerosis. These manifestations constitute a major challenge for clinicians involved in patient management. Moreover, several issues regarding the link between autoimmune rheumatic diseases and cardio pulmonary morbidity remain largely enigmatic. The mechanistic role of certain autoantibodies frequently observed in association with heart and lung diseases or the pathogenetic link between chronic inflammation and the pathways leading to atherosclerosis or pulmonary vascular changes are yet to be elucidated. As such, these questions as well as treatment strategies are of common interest to rheumatologists, immunologist, pulmonologists, and cardiologists and thus call for an interdisciplinary approach. This paradigm has been well established for rare conditions such as the Churg–Strauss syndrome. Nowadays, it seems that this approach should be expanded to encompass more common conditions such as coronary heart disease, pulmonary arterial hypertension or dilated cardiomyopathy. The present issue of Clinical Reviews in Allergy and Immunology addresses the new knowledge and concepts of autoimmune-related cardiopulmonary diseases. The issue derives from the 2010 International Autoimmunity Meeting held in Ljubljana, Slovenia and is thus timely and dedicated to the latest developments in this new multidisciplinary field.

Keywords Autoimmune · Heart · Lung · Cardiovascular · Autoantibdoies · Cytokines · Smoke

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The main systemic inflammatory and autoimmune diseases as defined by rheumatology textbooks are rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and systemic sclerosis (SSc). These autoimmune–rheumatic diseases have been strongly linked with an elevated cardiovascular risk, particularly when a state of hypercoagulability coexists in the form of the antiphospholipid syndrome (APS). However, until quite recently, the putative mechanisms by which concomitant cardiovascular manifestation occur could only be hypothesized and a generic role of chronic inflammation was postulated. In a similar fashion, several autoimmune diseases, particularly SSc [1–3] or Churg–Strauss syndrome (CSS) [4], almost invariably involve the lungs, while other diseases are less likely to cause a clinically significant pulmonary disease. In the case of pulmonary involvement, different mechanisms have been proposed, such as vasculitis of the lungs in the case of CSS, fibrosis in the case of SSc, and serositis in other conditions such as SLE.

The link between autoimmune–rheumatic diseases and cardiopulmonary morbidity has sparkled interest in recent years. Bibliometric data support this continuous interest as can be observed in a yearly PubMed search of the years 2000–2011 (Fig. 1). In this search, the term “autoimmunity” was utilized as the main search string and the base to determine the interest received by specific issues while publications identified by the additional use of the key

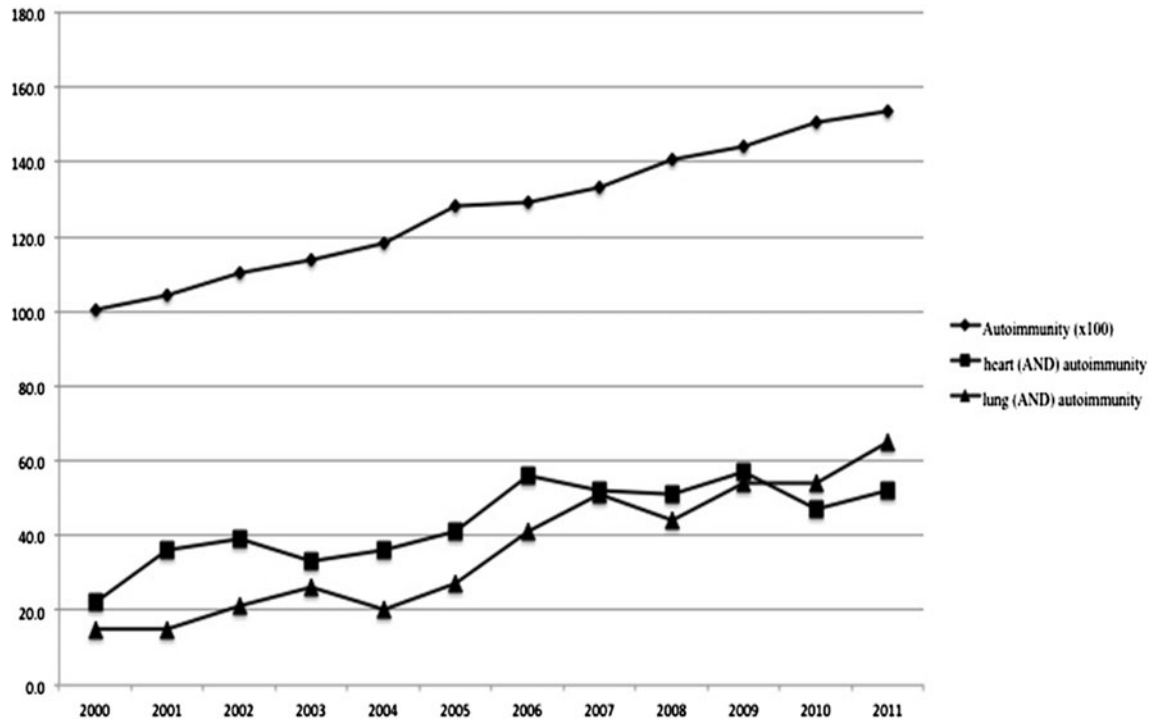

Fig. 1 PubMed search results, utilizing the term "autoimmunity" ($n \times 100$) as such or concomitantly with the terms "heart" or "lung"

words "heart" or "lung" represented the other two subgroups. All of which demonstrated a constant increase over the last decade.

The pathogenesis of cardiac and pulmonary comorbidities in autoimmune rheumatology remained enigmatic for many years. Recent complemented data from both clinical and basic research proposed new mechanisms that may shed some light on these linkages [5]. Three major mechanistic branches have been contemplated (1) the importance of autoantibodies mediated heart and lung involvement in these diseases and the potential of directed therapeutic interventions, (2) the part of other inflammatory mediators in determining organ involvement in autoimmune–rheumatic diseases, and (3) the role of antiphospholipids-related hypercoagulability and thrombosis. These three aspects were the center of numerous presentations and discussions held at the 2010 International Autoimmunity Meeting in Lubjiana, Slovenia.

In the case of autoimmune serology, new exciting data support a direct involvement of autoantibodies in the development of cardiovascular diseases. This was postulated for myocarditis and other heart conditions as dilated cardiomyopathy and ischemic heart disease in which an autoimmune pathogenesis had not been previously suspected. Intriguingly, these heart conditions have been demonstrated to share "an autoimmune serum profile" [6, 7], particularly following heart transplantation [8]. Candidate markers comprise of the antimyosin [9], anti-beta-1 adrenergic [10], anti-apoA1 [11], and anticardiac autoantibodies [12]. Furthermore, the growing evidence accumulated so far do not support these antibodies to represent mere epiphenomena but rather manifest a direct role for them in the pathogenesis of cardiac damage [13–20]. As a consequence, a therapeutic targeting was hypothesized in the case of anti-beta-1 adrenergic antibodies [10]. Notably, autoantibody cross-reactivity was also postulated with additional functional consequences in terms of heart rate or disease overlap [9]. A different scenario was proposed for idiopathic recurrent pericarditis. The latter pathogenesis is largely unknown, though genetically determined dysfunctions of the innate immune compartments have been considered [21]. Unraveling these new pathogenic scenarios enabled a new horizon of treatment options [22–25]. Biologics targeting of B cells may be promising in these conditions, given their relatively good safety profile and the experience gathered in different autoimmune–rheumatic diseases while new therapies directed at the innate response may also be considered [26–33]. Taking it all together, one may speculate that in the years to come individualized medicine will be applied in these settings [34–36] with the complementary data of genomics and epigenetics [37–40]. The role of both as well as the role of environmental factors has been clearly established in the pathogenesis of immune-mediated diseases. In the case of epigenetics, which link between genomic susceptibility and environmental factors [41, 42], constituents as DNA methylation, histone changes, and microRNA are ideal candidates for targeted approach. This has already been witnessed

in other fields in medicine as oncology and certain rheumatic diseases (i.e., rheumatoid arthritis) [43, 44]. In the same context, the National Institute of Environmental Health Sciences has recently reported the results of an expert workshop dedicated to define mechanisms [45], epidemiology [46], animal models [47], and criteria [48] for environmentally induced autoimmunity.

New inflammatory mediators were proposed to underlie the association between chronic inflammation and atherosclerosis or hypercoagulability in a number of autoimmune diseases [49] as SSc [50], liver autoimmune diseases [51, 52], and SLE [53, 54]. For instance, ferritin elevation is almost invariably encountered in chronic inflammation and is suggested to aid in the identification of patients at higher risk to develop thrombotic events in the context of SLE [55]. The involvement of iron metabolism in autoimmunity perpetuation is not a novel concept as it has already been suggested in hepatitis C-related autoimmune manifestations [56]. At the same time, an immune-mediated basis for pulmonary arterial hypertension was suggested following the observation that pro-inflammatory cytokines levels, such as interleukin 1 and 6, are elevated in the lung parenchyma of affected individuals [57]. The involvement of these interleukins was previously linked with immune tolerance breakdown [58, 59] in autoimmune liver disease [60] and Sjogren's syndrome [61] as well as with the complex Th17 cytokine network [14, 62]. Of note, limited impact of immune-mediated mechanisms was remarked in idiopathic pulmonary fibrosis in which immunosuppression had limited effectiveness [63]. Ultimately, we may expect that novel and current biological treatments that target these specific interleukins [64, 65] will be tested also in inflammatory heart and lung diseases.

Lastly, we are well aware that the frequent coexistence of antiphospholipids antibodies (APL) in patients with SLE and other connective tissue disease is a crucial factor in determining their cardiovascular risk [66]. Alas, very limited biomarkers are available to predict which patients will benefit from primary prevention of thrombotic events [67–71] or the catastrophic form of this syndrome [72, 73]. Thus, while we welcome the reappraisal of the pregnancy related risks of APL in a well-defined clinical setting [74], we are convinced that additional mechanisms and markers needs to be sought. In this aspect, the clinical phenotype of APS [55], the role of polyclonal IgG signatures [75] APL-related apoptosis [76], and specific manifestation such as atherosclerosis [66, 77] heart disease [78–80] pulmonary and other organ pathology [81, 82] may all be taken into consideration.

The impact of tobacco on autoimmune diseases warrants a specific discussion. Beyond its obvious damage to the lungs (e.g., chronic pulmonary obstructive disease) [83] smoking appears to parallel the geo-epidemiology of autoimmunity [84–87]. Furthermore, new data [88] have overtaken classical views in which, for example, tobacco smoke significantly increase the risk of RA by increasing peptide citrullination [89, 90]. These new data include the significant impact of tobacco smoke on numerous cytokines and inflammatory key mediators in RA as TNF-alpha and IL-1.

In conclusion, we are convinced that future studies will provide increasing evidence on the link between cardiopulmonary morbidity and autoimmune–rheumatic diseases. These links are expected to work in two directions, on the one hand to establish an autoimmune base for heart and lung conditions previously not associated with immune mediated processes and on the other to elucidate new mechanisms for cardiac and pulmonary phenotypes of systemic autoimmune conditions. Ultimately, this is expected to provide new markers that are ideal candidates for diagnosis, risk assessment, and treatment targeting.

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