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Editorial

Sarcoidosis Phenotypes

Fenotipos en sarcoidosis

Sarcoidosis is a systemic granulomatous disease of unknown cause that predominantly affects young and middle-aged adults. Intrathoracic involvement including lymphatic nodes and lungs accounts for more than 90% of the cases.[1] Its diagnosis is not standardized; however, it should include a compatible clinical presentation, histopathologic findings of non-necrotizing granulomatous inflammation (not always required, as in Löfgren's syndrome, lupus pernio or Heerfordt's syndrome) and the exclusion of an alternative diagnosis.[2]

Disease presentation, natural history and prognosis are highly variable. For example, sarcoidosis cohorts differ in terms of age, sex, ethnicity, and organ involvement. Clinical course ranges from spontaneous resolution to disabling chronic disease, through pulmonary fibrosis, renal failure, cardiac involvement or neurosarcoidosis. This variability may reflect the difference in genetic background, environmental exposure, and socioeconomic status; outlining what we call phenotypes.[3]

A phenotype is defined as the observable properties of an organism that are produced by the interactions of the genotype and the environment. In this setting, observable properties mean the clinical, functional, imaging, and biological features of the disease. When adding molecular pathways, this phenotype becomes an endotype.[4,5]

Nevertheless, despite the terminological peculiarities, phenotyping is part of the quest for personalized medicine.[5,6]

Löfgren's syndrome might be one of the best examples of a sarcoidosis phenotype. It predominates in women and is characterized by acute on set of fever, bilateral hilar lymphadenopathy, erythema nodosum and/or bilateral arthritis of the lower extremities, usually presenting over spring season. Approximately 70% of the patients express the allele HLA-DRB1*0301/DQB1*0201. Patients expressing this allele have almost 100% of recovery after 2 years.[1,4] In contrast, patients with high-risk phenotype, which includes refractory lung disease with fibrosis and/or pulmonary hypertension, as well as cardiac, neurological, or multi-organ involvement, have a poor prognosis.

Previously, one of the firsts attempts of phenotyping sarcoidosis was the Scadding stages[7]; however, despite its relevance, these stages cannot explain by itself other aspects of the disease[8] as reflected in the lack of correlation of the chest X-ray with pulmonary function tests.[9,10]

Advances in diagnosis techniques have changed the way of phenotyping in sarcoidosis. High resolution computed tomography (HRCT) scans and 18-2-Fluoro-2-deoxy-ᴅ-glucose Positron Emission Tomography (FDG-PET) are tools that in combination with other clinical features like pulmonary function tests (PFTs), lymphocyte count on bronchoalveolar lavage (BAL), organ-specific laboratory tests and questionnaires of quality of life (QoL) help clinicians to evaluate morphologic disease extension, metabolic activity, organ affection severity, prognosis, and impact.

In 2018, the GenPhenReSa (Genotype–Phenotype Relationship in Sarcoidosis) project, presented the results of its multicentric study which included 2163 patients with sarcoidosis recruited at 31 centres along Europe. Using a cluster analysis, the authors described the abdominal phenotype, which included renal, splenic, and hepatic affection. Additionally, they described the ocular–cardiac–cutaneous–central nervous system (CNS) [OCCC], the musculoskeletal-cutaneous, the pulmonary lymphonodal and the extrapulmonary phenotype.[3]

Phenotyping according to organ involvement opens the possibility to study genetic markers on those patients with different clusters of organs manifestation. Recently, from the GenPhenReSa cohort, significant associations of some well-known related to sarcoidosis single nucleotide polymorphisms (SNPs) were found in association with the type of onset (acute or subacute) and with a severe disease course.[11]

Also, phenotyping can have therapeutic implications, not only influenced from the shared organ pathophysiology in a single phenotype, but also derived from different clinical courses. Regarding this, a recent Delphi consensus on treatment developed a schema to direct therapy considering different levels of treatment depending on the clinical course phenotype (acute, chronic, or advanced).[12,13]

The use of "omics" has improved the understanding of many diseases.[6] Beyond the classic omics, a new concept of integration of imaging data with blood or tissue transcriptomics[14] "the radiotranscriptomics" link the expression of different genes with different measurable radiological manifestations.[15] Radiotranscriptomics may be interesting in pulmonary sarcoidosis research. Associating systemic transcriptomics with quantitative imaging biomarkers and lung activity by FDG-PET scan may help to identify surrogate systemic markers of lung damage to improve disease management and predict prognosis.

In conclusion, sarcoidosis phenotyping still provides limited information. Clinical phenotyping has been the focus of many studies; however, the inclusion of genetic and molecular pathways is still scarce. From a clinical point of view, phenotypes can help to

address treatments, however, if we want to prevent or predict disease prognosis, we still need to investigate further areas.

New approaches to establish more than clinical phenotypes are needed in this complex and heterogeneous disease. Clinical course, organ affection clusters, genetic profiles and more recently, radiomics and transcriptomics need to be combined in order to advance in personalized medicine of sarcoidosis.

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Conflicts of interest

The authors have no conflicts of interest in this study.

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