Sarcoidosis has been characterized by a pre-dominant T-Helper 1 (Th1) granulomatous process based not only the pathology seen, but also on the cell cytokine profile (1). Even this statement now is debated. New data shows a Th2/M2 skewing in the granulomas found in neuromuscular sarcoidosis (2). Also, it has been demonstrated that Th2/M2 favors cell aggregation and giant cell formation in muscular sarcoidosis (3). These evolving observations highlight the many unknowns that remain about this disease. Some of the unknowns include the identification of agents that provoke the response, as well as specifics of how genetics, interacting with these unknown causative agents, give rise to the diverse clinical phenotypes that are seen in this disease (4). To optimize research and its translation to the recognition and delivery of care to those affected with this disease, it is critical that we consider socioeconomic factors and their effects on vulnerable/minority populations (5).

Background

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The Evolution of Sarcoidosis Research at the Cellular Level

Based on previously published findings that blockade of the programmed death-1 pathway restores sarcoidosis CD4+ T-Cell proliferative capacity (6), Wonder Drake MD, Vanderbilt University, examined targeting TH17/Treg dysfunction to halt progression of pulmonary sarcoidosis. Specifically, she discussed her group’s research on PD-1 up-reg-
ulation on CD4+ T cells and how this up-regulation may lead to increased TH17 cells that produce IL-17A and TGF-beta1 and ultimately may induce fibrosis. Andrew Fontenot MD, University of Colorado, outlined his group’s research identifying T cell epitopes in human disease and its application to defining the antigen in sarcoidosis. Larry Schlesinger MD, The Ohio State University, lectured on modeling of the granuloma using TB as the initial “model,” and compared the features of this model to a sarcoidosis granuloma model hoping a better granuloma model for sarcoidosis may be useful in the discovery and translation of disease mechanisms and treatment. This could address areas such as cell signaling, and polarization of macrophages into M1 or M2 phenotypes, and related disease implications. Ginger Spritzer, Director of the Foundation for Sarcoidosis Research (FSR) and Dan Culver MD, Cleveland Clinic, a member of the scientific advisory board for FSR, laid out the FSR’s recently awarded grants for sarcoidosis research. These included three $150,000 grants for models in sarcoidosis: 1) Thomas Weichart PhD, University of Vienna, for characterization and improvement of a novel mouse model that spontaneously develops progressive sarcoidosis by chronic activation of mTORC1; 2) Elliot Crouser MD, The Ohio State University, to explore mechanisms of early granuloma formation using a novel in vitro model of sarcoidosis; and 3) Simon Hart, MBChB, PhD, Hull York Medical School, UK, for development and application of a multi-scale computational model of sarcoidosis.

**Sarcoidosis from a genetic perspective**

Courtney Montgomery PhD, Oklahoma Medical Research Foundation, discussed how sarcoidosis associated genes are related to other inflammatory and autoimmune diseases and that different genetic variants affect the risk of specific sarcoidosis phenotypes. Edward Chen MD, John Hopkins University, presented further information from the NIH-sponsored Genomic Research in Alpha-1 Antitrypsin deficiency and Sarcoidosis (GRADS) Study (7). He anticipates a new phenotypic classification based on integrative assessment of clinical, demographic, genomics, and microbiological data developed from GRADS.

**Focus on disadvantaged and at-risk populations**

In the United States, sarcoidosis affects a disproportionate number of African Americans. Nad-era Sweiss, MD, of the University of Chicago, discussed that African Americans die at an earlier age than Caucasians with a 12 times higher age-adjusted mortality rate (8). Factors which may account for these differences are limited access to quality care, fragmented and episodic care, financial constraints, inability to adhere to medical treatment plans and gaps in health provider’s capacity to accurately predict disease progression and adverse outcomes. Alicia Gerke, MD, MBA, University of Iowa, explained how “knowledge networks” may improve sarcoidosis care, especially in minority and disadvantaged patients. She described actual cases that have been addressed on the Sarcoidosis List Serve (sarcoid-list@uioowa.edu), an e-mail-based forum for physicians, including sarcoidosis experts, to share information and to obtain useful advice without divulging proprietary patient information. Rich Bernstein MD, Penn State Health, College of Medicine, examined the barriers to diagnosis and treatment of inner-city sarcoidosis patients in Central Pennsylvania, despite close proximity to a tertiary regional medical center. More research is needed to define and help overcome these barriers.

**Fatigue and quality of life**

Fatigue is the most common symptom described in sarcoidosis patients, affecting upwards of 2/3 of sarcoidosis patients altering quality of life independent of granulomatous activity (9). Marc Judson MD, University of Albany, summarized clinical and research tools used to more accurately quantify sarcoidosis-induced fatigue. He also outlined the use of Item Response Theory PROs which may be faster, less cumbersome and more accurate than the traditional fatigue questionnaires. In an effort to gain insight from other disciplines, Walter Royal III, MD, Professor of Neurology, University of Maryland, discussed cognitive failure and fatigue focusing on how lessons learned from multiple sclerosis can be applied to sarcoidosis. Eva Carmona MD, PhD, Mayo Clinic, discussed the analysis of Quality of Life (QOL)
from the Registry for Sarcoidosis Associated Pulmonary Hypertension (ReSAPH) database.

Neuro, cardiac and other extreme clinical manifestations of sarcoidosis

The clinical area featured at this year’s AASOG meeting was neurosarcoidosis, including central nervous system and peripheral manifestations, particularly small fiber neuropathy (SFN) (10). Divpreet Kaur MD, Penn State Health, College of Medicine, reviewed the challenges confronted by providers seeking to establish the diagnosis of small fiber neuropathy. Dan Culver MD, Cleveland Clinic discussed novel therapeutic approaches, including ARA290, an erythropoietin-like compound under investigation as a therapeutic agent for SFN in sarcoidosis (11). Carlos Pardo-Villamizar MD, Johns Hopkins, reviewed how sarcoidosis mimics other neurologic conditions. Tao Ouyang, Penn State Health, College of Medicine, gave examples of the wide range of neuroimaging findings seen in sarcoidosis. Dr. Pardo-Villamizar presented a second session, describing potential biomarkers that may find application in neurosarcoidosis. Elliot Crouser MD, the Ohio State University, discussed early detection and treatment of active cardiac sarcoidosis, focusing on cardiac FDG-PET and cardiac MRI. He reviewed new data on circulating exosomes as potential bio-markers in cardiac sarcoidosis, which, if proven reliable, would reduce costs in diagnosing cardiac sarcoidosis. Laura Koth MD, University of San Francisco, gave an outline of the USF experience with sarcoidosis.

Lessons learned from a historical and other research standpoint

Herbert Reynolds MD, Penn State Health, College of Medicine, one of the early pioneers in sarcoidosis research on a cellular level, gave the keynote address on a historical perspective of sarcoidosis. Rebecca Bascom MD, Penn State Health, College of Medicine, talked about how lessons learned from the IPF registry may be useful in the continued development of sarcoidosis registries. Lisa Maier MD, MSPH, National Jewish Health, outlined the possible associated occupational and environmental causes of sarcoidosis from a number of studies; including increased risk associated with musty odors, use of insecticides, exposure to air conditioning, and exposure to birds.

Poster presentations

As has become a traditional part of the AASOG annual meeting, five Speaker Awards were presented to the top abstracts from physicians and scientists in training. The winners are as follows: Brad Brasher, Medical University of South Carolina, “Preliminary Evaluation of a Fatigue Self-Efficacy Scale in Sarcoidosis”; Efstratios Koutroupakis, Department of Medicine, Albany Medical Center, “Assessment of Cough in Sarcoidosis and Correlation of the Leicester Cough Questionnaire with a Novel Visual Analog Scale”; Landon W. Locke, The Ohio State University, “Alternatively Activated (M2) Macrophage Polarization and the Sarcoidosis Immune Paradox”; Megan H. Noe, Department of Dermatology, Perelman School of Medicine, University of Pennsylvania, “High frequency ultrasound: a novel instrument to quantify granuloma burden in cutaneous sarcoidosis”; Ashley E. Pender, Department of Medicine, Feinberg School of Medicine, Northwestern University “An FDG-PET/CT-guided Strategy for Adjustment of Immunosuppressive Therapy of Cardiac Sarcoidosis”.

References

1. Baughman RP, Culver DA, Judson MA. A Concise Review of Pulmonary Sarcoidosis. Am J Respir Crit Care Med 2011; 183: 573-581.
2. Prokop S, Heppner FL, Goebel H, Stenzel W. M2 Polarized Macrophages and Giant Cells Contribute to Myofibrosis in Neuromuscular Sarcoidosis. Am J Pathol 2011; 178: 1279-1286.
3. Preusse C, Goebel H, Pehl D, Rinnenthal JL, Kley RA, Allenbach Y, Heppner FL, Vorged M, Authier FJ, Gherardi R, Stenzel W. Th2-M2 immunity in lesions of muscular sarcoidosis and macrophagic myofasciitis. Neuropathol Appl Neurobiol 2015; 41: 952-963.
4. Pereira CA, Dornfeld MC, Baughman R, Judson MA. Clinical phenotypes in sarcoidosis. Curr Opin Pulm Med 2014; 20: 496-502.
5. Groman R, Ginsburg J. Racial and Ethnic Disparities in Health Care: A Position Paper of the American College of Physicians. Annals of Intern Med 2004 3; 141: 226-232.
6. Braun N, Celada L, Herazo-Mayar J, Abraham S, Shaginurova G, Servin, C, et al. Blockage of the Programmed Death-1 Pathway Restores Sarcoidosis CD4+ T-Cell Proliferative Capacity. Am J Resp Crit Care Med 2014; 190: 560-571.
7. Muller DR, Koth LL, Maier L, Morris A, Drake W, Rosman M, Leader J, et al. Rationale and Design of the Genomic Research in al-
pha-1 antitrypsin Deficiency and Sarcoidosis (GRADS) Study- Sarcoidosis Protocols. Ann of the Am Thorac Society 2015;12: 1561-1571.
8. Mirsaedi M, Machado RF, Schraufnagel D, Sweiss N, Baughman R. Racial Difference in Sarcoidosis Mortality in the United States. Chest 2015; 147: 438-449.
9. Michielsen H, Drent M, Peros-Bolubicic T, De Vries J. Fatigue is associated with quality of life in sarcoidosis patients. Chest 2006; 130: 989-994.
10. Tavee J, Culver D. Sarcoidosis and small-fiber neuropathy. Curr Pain Headache Rep 2011; 15: 201-206.
11. van Velzen M, Heij L, Nieters M, Cerami A, Dunne A, Dahan A, Brines M. ARA 290 for treatment of small fiber neuropathy in sarcoidosis. Expert Opin Investig Drugs. 2014; 23: 541-50.