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LETTER TO THE EDITOR

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Hidden relationship between sarcoidosis and gut microbiota: recent evidence and future implications

Ramadan Abdelmoez Farahat[1], Abubakar Nazir[2], Sidhant Ochani[3], Sheharyar Hassan Khan[2], Annama Mahjabin[4], Saleh Mohammed[5], Israt Jahan[4], Khadizatul Kubra[6], Sarya Swed[7*] and Kuldeep Dhama[8*]

Dear Editor,

Sarcoidosis, a multi-system disease with unspecified causes, is attributed to non-necrotizing granulomas formation with epithelioid cells in several body organs [1]. It affects patients irrespective of race and age but usually, it targets adults aged between 30 and 50 years. Its incidence ranges between 2 and 11 per 100,000 individuals per annum [2]. Various factors, including genetic predisposition, infection, environmental factors, adverse effects of drugs, autoimmunity, and exposure to insecticides, can lead to sarcoidosis. The 11 risk loci associated with sarcoidosis are HLA-B, BTNL2, ANXA11, HLA-DPB1ATXN2, IL23R, NFKB1, IL12B, chromosome 11q13.1, FAM177B, and RAB23 [3]. Transforming growth factor β (TGF-β), Toll-like receptor 4 (TLR-4), and tumor necrosis factor α (TNF-α) increase the susceptibility to sarcoidosis [4]. Mycobacterium usually triggers infection-mediated sarcoidosis. Mycobacterium contains proteins like Kat G and ESAT-6, making it a potential causative agent of sarcoidosis. Leptospira, herpes virus, retrovirus, and *Borrelia burgdorferi* can lead to sarcoidosis by eliciting a persistent T cell immune response. Patients having hepatitis C virus infection, when treated with interferon α therapy, may develop sarcoidosis [5]. The symptoms of sarcoidosis range from an asymptomatic to a progressive or relapsing state resulting in pulmonary dysfunction mainly due to pulmonary fibrosis and sudden cardiac death in case of cardiac involvement. The involvement of multiple organs results in diagnostic uncertainty. However, some clinical features like Lofgren syndrome, Heerfordt syndrome, and lupus pernio are salient presentations of sarcoidosis. The combination of ankle arthritis, erythema nodosum, and mediastinal lymphadenopathy is termed Lofgren syndrome. The triad of uveitis, parotitis, and mediastinal lymphadenopathy is Heerfordt syndrome. If it involves the skin, then it is called lupus pernio [6]. In 25–50% of cases, extrapulmonary symptoms like skin lesions, uveitis, liver involvement, abdominal lymphadenopathy, and peripheral arthritis occur frequently. Cardiac and neurological symptoms are among the early indications of sarcoidosis. Other indications like bilateral parotitis, nasosinusal and laryngeal signs can also occur in sarcoidosis but only 10% of patients exhibit them. Hypercalcemia and renal dysfunction are also common in sarcoidosis [1].

Microbes that live in an ecosystem are called microbiota. Normal human microbiota includes archaea,

*Correspondence:
Sarya Swed
saryaswed1@gmail.com
Kuldeep Dhama
kdhama@rediffmail.com
[1] Faculty of Medicine, Kafrelsheikh University, Kafrelsheikh, Egypt
[2] Department of Medicine, King Edward Medical University, Lahore, Pakistan
[3] Department of Medicine, Khairpur Medical College, Khairpur Mirs, Pakistan
[4] Department of Public Health, Chattogram Veterinary and Animal Sciences University, Chattogram, Bangladesh
[5] Department of Medicine, Faridpur Medical College, Faridpur, Bangladesh
[6] Department of Chemistry, Jahangirnagar University, Dhaka, Bangladesh
[7] Faculty of Medicine, Aleppo University, Aleppo, Syria
[8] Division of Pathology, ICAR-Indian Veterinary Research Institute, Bareilly, Izatnagar, Uttar Pradesh 243122, India

eukarya, bacteria, fungi, yeast, parasites, viruses, helminths, protozoa, etc. They are widespread through the internal cavities of the body, with more than 95% being in the gut [7]. These gut microbiota have several beneficial impacts on human beings, i.e., nutrients and drug metabolism, harvesting energy, protection against pathogens, maintaining the gut structural integrity, shaping the intestinal epithelium and immunomodulation along with the associated imbalance that has been significantly found to have a role in multiple human disorders such as diabetes, obesity, rheumatoid arthritis, and several autoimmune diseases (Fig. 1) [8]. These microbes start to colonize the sterile gastrointestinal (GI) tract depending on food intake, breastfeeding, and mode of delivery it is believed that the gut microbiota may influence future diseases and some studies have highlighted the association between increased infections and allergic diseases [9, 10]. Now it is also believed that a human is not born sterile and the process of colonization is an evolutionary process, which is gradual, dynamic, complex, and in continuous development throughout years parallel to the development of the immune system of the newborn [11]. Microbial dysbiosis or imbalance in gut microbiota is associated with disorders such as interstitial lung diseases (ILDs). The lung has been considered a sterile environment for many years; however, recent microbial sequencing techniques suggest that several microbiotas are present in lower and upper respiratory tracts, and their composition is changed in respiratory diseases [12].

However, apart from the lung microbiota that directly affects respiratory homeostasis, the gut microbiota also plays a significant role in the development and progression of respiratory diseases. Similarly, there is evidence [13] that transitions in the lung flora affect gut functioning as well, and such a relationship between these two systems is explained by what is known as the gut-lung axis. The primary mechanism by which the gut flora affects the lungs is through dysbiosis in the gut flora resulting from drugs, diseases, diet, smoking, or may be due to changes in the local gut microbiota. Such disturbances eventually result in changes in host immune responses, activation of immune modulators, and activation of tissue damage pathways that remain confined to the GI tract and the lungs, causing various lung pathologies. One such example is sarcoidosis, where alterations in the gut microbiota result in the activation and secretion of proinflammatory cytokines (IL-6, IL-12, IL-18, and TNF-α) and promote the formation of granulomas in various organs. Apart from sarcoidosis, gut microbiota also influences the pathogenesis of asthma, hypersensitivity pneumonitis, pneumonia, silicosis, and systemic sclerosis [14]. Contrary to the evidence that a gut microbiota-influenced immune response is responsible for the granuloma development in sarcoidosis, there were speculations of direct microbial involvement in the development of sarcoidosis (microbial theory). However, there is no clear evidence that refutes or supports this theory but one of the studies by Negi et al. [15] attributes the role of *Cutibacterium acnes* (*C. acnes*), a commensal colonizing skin that may be found throughout the GI tract and is extracted from granulomas sample tissues from patients of sarcoidosis. Such data provides significant implications

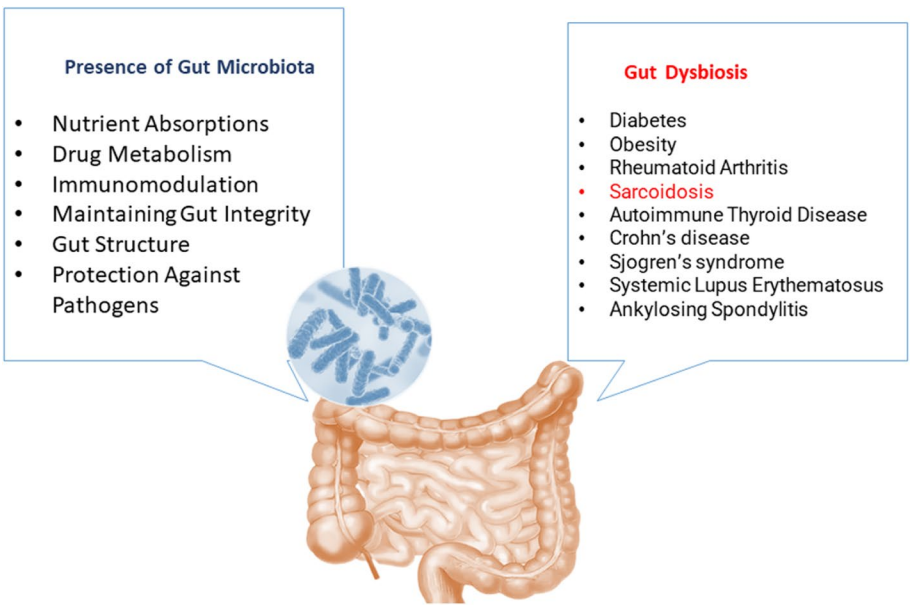

Fig. 1 The relation between the presence or absence of microbiota and gut function

for the treatment options for sarcoidosis, which is managed conservatively. Apart from the evidence showing C. acnes' involvement in the granuloma formation in sarcoidosis, there are other microbes more specific to the gut microbiota that interacts with pulmonary sarcoidosis. Nasiri et al. [16] noted significant changes in the composition and quantities of gut microbiota particularly Bifidobacterium in murine models of sarcoidosis indicating a significant relationship between gut microbiota and sarcoidosis. Despite these pieces of evidence [17], the consensus as per the current evidence does not support a causal relationship between these pathogens and sarcoidosis, and future studies are required to accurately demarcate any role of pathogens in the disease process. Apart from the direct role of pathogens in the pathogenesis of sarcoidosis, several other factors have been seen to have an association with gut microbiota and diseases, which include genetic factors as the bacteria synthesize different metabolites based on different genetic makeup, maintaining a stable environment, and sex differences as the microbiota have been seen to have a role in regulating sex hormones that can affect a particular sex-based severity of auto-immune diseases [5]. Additionally, they are found to regulate and synthesize neurotransmitters and release cytokines, stimulating intestinal lymphocytes and modulating different immune responses in various ways. The advances in the development of technologies are offering opportunities to understand the role of microbiota and disease development. Sarcoidosis is a disease of unknown etiology causing organ-specific autoimmune diseases and has a disease speculative mechanism which is believed to include the role of microbial patterns to initiate immune processes [9]. However, the findings are controversial because, for a long time, it was hypothesized that the microorganisms have a role in developing sarcoidosis based on the presence of DNA and other microbial components in biosamples and several studies were unable to reveal such association and unclear whether the microbial patterns have no role in the development of diseases or if the applied methodologies have limitations [18]. The exact role of pathogenesis and microbial patterns is unclear; however, they may have a role in initiating the formation of persistent, granulomatous inflammation, thus, investigating the role of hidden correlation between sarcoidosis and microbiota can open new avenues for searching and tackling the cause of disease. Autoimmune diseases may occur before as well as following diagnosis with sarcoidosis, but the prevalence of co-existing is unknown due to scarce literature. Several studies have reported increased frequency, prevalence, and combination of several diseases like systemic lupus erythematosus, autoimmune thyroid disease, Sjogren's syndrome, Crohn's disease, and ankylosing spondylitis [19, 20]. Considering the autoimmune nature of sarcoidosis, a systematic diagnostic evaluation is of paramount importance to detect overlapping diseases accompanying sarcoidosis. Despite limited literature, the available research articles weigh more towards supporting the fact that the imbalance of gut microbiota has an impact on the pathogenesis of various autoimmune diseases in both animals and humans compared to healthy ones [7, 11]. The imbalance and altered composition of these microbes can affect the gut immune system, including intestinal inflammation, defective antigen tolerance to food, and enhanced permeability of the gut. As aforementioned, the maintenance of gut integrity is essential since the gut and mucosal barrier can allow these microbes to enter the systemic blood, thus leading to system immune hyperactivation by inducing an imbalance of host immune homeostasis [11]. Therefore, further future research is needed to identify, and search for principal sources, inflammatory processes caused by gut microbiota, new therapeutic targets, and biomarkers, and to understand the positive and negative effects of these gut microbes on human health amidst a considerable increase in autoimmune and inflammatory disease worldwide.

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Authors' contributions
RAF: the conception and design of the study. RAF, AN, SO, AM, SM, IJ, SHK, and KK: acquired information, drafted the article, and designed the figures. RAF, SHK, SS, and KD: interpretation of data and revising it critically for important intellectual content. All the authors gave final approval of the version to be submitted.

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Declarations

Competing interests
The authors declare that they have no competing interests.

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