Why would immunooendocrino-senesence, age-related changes in the gut microbiota and susceptibility to infection favour polymyalgia rheumatica over seronegative elderly-onset rheumatoid arthritis?

Sirs,

We are intrigued by Coskun Belindayi’s review article in which the author proposed that immunosenescence/inflammaging, increased risk of infections with aging, endocrino-senesence, and age-related changes in gut microbiota are factors associated with polymyalgia rheumatica (PMR) and aging (1).

We appreciate the views of Coskun Belindayi; however, the aforementioned factors are not exclusive to PMR. Indeed, they have been potentially linked with other elderly-onset inflammatory rheumatic diseases, including seronegative elderly-onset rheumatoid arthritis (SEORA) (2).

The relationship between PMR and SEORA has been variously interpreted over the years. Nowadays, data allow PMR and SEORA to be classified as nosographically distinct (3,5). Specifically, erosive arthritis and symmetrical involvement of metacarpophalangeal joints are absent in patients with PMR (6). Additionally, PMR can be associated with giant cell arthritis (GCA) about in 20% of cases, whereas association of GCA with SEORA is exceptional (7). Recently, some researchers proposed the acronym GPSD, that is GCA-PMR spectrum disease, considering GCA and PMRA as a continuum (8).

On the other hand, the fact that an initial diagnosis of PMR may change to SEORA and vice versa during follow-up, and that SEORA patients may have PMR features at onset (so-called “SEORA with PMR-like onset”) emphasizes that PMR and SEORA have many similarities so that it can be difficult to differentiate these diseases each from other (9,10).

We recognise that a few studies involved a head-to-head comparison between SEORA and PMR pathogenesis (2,4,8,9). Immunosenescence/inflammaging, the so-called “endocrine-senesence”, and age-related changes in gut microbiota seem to be common in older adults. If so, why would immunooendocrine-senesence, and age-related changes in the gut microbiota favour PMR over SEORA?

Concerning the role of antigenic stimuli carried by infectious agents, the published literature recently reported cases of PMR and SEORA following infectious diseases, including SARS-CoV-2. Without a doubt, increased infection risk in the older population might serve as a triggering factor in the development of PMR. However, we are unsure whether it is true PMR or something similar such as “PMR-like syndromes”. For instance, some researchers speculated that PMR triggered by an infectious agent could be a distinct subset of the disease characterised by milder clinical manifestations and faster glucocorticoid responses (11).

Therefore, it is not trivial to focus on the role of genetic background and epigenetic regulation. Due to advance in genome sequencing, several loci linked to an increased risk of RA have been discovered. In short, the human leucocyte antigen (HLA)-DRB1*01 and -DRB1*10 alleles have been associated with an increased risk of RA; HLA-DRB1*04 and -DRB1*13/14 are more closely associated with PMR (12,13). The HLA association with PMR or SEORA should take ethnicity into account, as differences exist in European, Asian and African populations. Regarding epigenetic regulation, single nucleotide polymorphisms (SNPs) of interleukin 23 (IL-23) receptors were found to be capable of regulating critical pathways involved in SEORA but not PMR pathogenesis. Some micro(mi)RNAs, such as mi-r-22, play different roles in SEORA and PMR patients (2).

The genetic and epigenetic background might, therefore, partly explain the differences between the two diseases in terms of inflammatory infiltrates. For instance, a predominance of autoinflammatory aspects has been observed in PMR with histological studies showing the aberrant activation of innate immune cells (i.e. macrophages) with poor lymphocyte infiltration, few neutrophils and no natural killer (NK) cells (14). On the contrary, NK cells and B cells are present in the synovial fluids of RA patients and a strong correlation with severity and disease duration has been documented (15) NK cells are considered to be important in bone destruction that is, by definition, absent in PMR.

In conclusion, as Coskun Belindayi’s article highlighted, we have some pieces of a whole that, unlike Rubik’s cube, we cannot assemble. The provocative question in our title should suggest new, different methodological approaches stimulating research into genetic, epigenetic and immune-histopathological studies comparing PMR and SEORA patients. We share Coskun Belindayi’s hope that future research adds newer distinguishing elements, relevant to clinical practice.

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