Why would immuno- and endocrino-senescence, 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 Benlidayi's review article in which the author proposed that immunosenescence/inflammaging, increased risk of infections with aging, endocrinosenescence, 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 arteritis (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 PMR and GCA 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") emphasises 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-senescence", and age-related changes in gut microbiota seem to be common in older adults. If so, why would immuno- and endocrino-senescence, and age-related changes in the gut microbiota favour PMR over SEORA?

Concerning the role of antigenic stimulus 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 miR-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.

C. Manzo[1], *MD*
A. Nune[2], *MD*
A. Castagna[3], *MD, PhD*

[1]Division of Rheumatology, Internal and Geriatric Medicine Department, Azienda Sanitaria Locale Napoli 3, Health District no. 59, Sant'Agnello, Italy;
[2]Department of Rheumatology, Southport and Ormskirk Hospital NHS Trust, Southport, UK;
[3]Primary Care Department, Azienda Sanitaria Provinciale Catanzaro, Soverato, Italy.

Please address correspondence to:
Ciro Manzo
Division of Rheumatology,
Internal and Geriatric Medicine Department,
Azienda Sanitaria Locale Napoli 3,
Health District no. 59,
80065 Sant'Agnello (NA), Italy.
E-mail: manzoreumatologo@libero.it

Competing interests: none declared.

Clin Exp Rheumatol 2023; 41 (Suppl. 135): S25-26.

References

1. COSKUN BELINDAYI I: Why is polymyalgia rheumatica a disease of older adults? Explanations through etiology and pathogenesis: a narrative review. *Clin Rheumatol* 2023 Jul 20. https://doi.org/10.1007/s10067-023-06708-3
2. WU J, YANG F, MA X, LIN J, CHEN W: Elderly-onset rheumatoid arthritis vs. polymyalgia rheumatica: Differences in pathogenesis. *Front Med* (Lausanne) 2023; 9: 1083879. https://doi.org/10.3389/fmed.2022.1083879
3. OHTA R, SANO C: Differentiating between seronegative elderly-onset rheumatoid arthritis and polymylgia rheumatica: a qualitative synthesis of narrative reviews. *Int J Environ Res Public Health* 2023; 20(3): 1789. https://doi.org/10.3390/ijerph20031789
4. MANZO C, EMAMIFAR A: Polymyalgia rheumatica and seronegative elderly-onset rheumatoid arthritis: two different diseases with many similarities. *Eur Med J Rheumatol* 2019; 4: 111-9.
5. CEDENO M, MURILLO-SAICH J, CORAS R *et al.*: Serum metabolomic profiling identifies potential biomarkers in arthritis in older adults: an exploratory study. *Metabolomics* 2023; 19(4): 37. https://doi.org/10.1007/s11306-023-02004-y
6. SALVARANI C, CANTINI F, OLIVIERI I: Distal musculoskeletal manifestations in polymyalgia rheumatica. *Clin Exp Rheumatol* 2000; 18 (Suppl. 20): S51-52.
7. PEASE CT, HAUGEBERG G, MORGAN AW *et al.*: Diagnosing late onset rheumatoid arthritis, polymyalgia rheumatica, and temporal arteritis in patients presenting with polymyalgic symptoms. A prospective longterm evaluation. *J Rheumatol* 2005; 32(6): 1043-6.
8. DEJACO C, DUFTNER C, BUTTGEREIT F et al. The spectrum of giant cell arteritis and polymyalgia rheumatica: revisiting the concept of the disease. *Rheumatology* (Oxford) 2017; 56: 506-15. https://doi.org/10.1093/rheumatology/kew27
9. OLIVO D, D'AMORE M, MATTACE-RASO F, MATTACE R: Clinical and laboratory features at onset of polymyalgia rheumatica (PMR) and elderly onset of rheumatoid arthritis in PMR-like presentation: a comparison of two groups of patients. *Arch Gerontol Geriatr* 1996; 22 (Suppl. 1): 527-33. https://doi.org/10.1016/0167-4943(96)86994-9
10. CUTOLO M, CIMMINO MA, SULLI A: Polymyalgia rheumatica vs late-onset rheumatoid arthritis. *Rheumatology* (Oxford) 2009; 48(2): 93-5. https://doi.org/10.1093/rheumatology/ken294
11. FALSETTI P, CONTICINI E, ACCIAI C *et al.*: Polymyalgia rheumatica following infective triggers or

vaccinations: a different subset of disease? *Reumatologia* 2020; 58(2): 76-80. https://doi.org/10.5114/reum.2020.95360
12. STAHL EA, RAYCHAUDHURI S, REMMERS EF *et al*.: Genome-wide association study meta-analysis identifies seven new rheumatoid arthritis risk loci. *Nat Genet* 2010; 42: 508-14. https://doi.org/10.1038/ng.582
13. HYSA E, GOTELLI E, SAMMORI S *et al*.: Immune system activation in polymyalgia rheumatica: which balance between autoinflammation and autoimmunity? A systematic review. *Autoimmun Rev* 2022; 21(2): 102995. https://doi.org/10.1016/j.autrev.2021.102995
14. MELICONI R, PULSATELLI L, UGUCCIONI M *et al*.: Leukocyte infiltration in synovial tissue from the shoulder of patients with polymyalgia rheumatica. Quantitative analysis and influence of corticosteroid treatment. *Arthritis Rheum* 1996; 39(7): 1199-207. https://doi.org/10.1002/art.1780390719
15. YAMIN R, BERHANI O, PELEG H *et al*.: High percentages and activity of synovial fluid NK cells present in patients with advanced stage active rheumatoid arthritis. *Sci Rep* 2019; 9(1): 1351. https://doi.org/10.1038/s41598-018-37448-z