Editorial paper

Reumatologia 2023; 61, 1: 1-3
DOI: https://doi.org/10.5114/reum.2023.124336

Polymyalgia rheumatica and cancer: surveillance duration and other points to ponder

Ciro Manzo[1], **Arvind Nune**[2]

[1]Rheumatologic Outpatient Clinic, Health District no. 59, Azienda Sanitaria Locale Napoli 3, Sant'Agnello, Italy

[2]Department of Rheumatology, Southport and Ormskirk Hospital NHS Trust, Southport, United Kingdom

Introduction

Polymyalgia rheumatica (PMR) is one of the most common inflammatory rheumatic disease affecting the elderly [1]. Up to 20% of patients with PMR may develop giant cell arteritis (GCA), a primary granulomatous vasculitis affecting the aorta and its branches. The association of PMR with GCA, also known as "Horton's disease", has therapeutic and prognostic consequences [2].

The possibility that isolated PMR can be a paraneoplastic syndrome has long been debated with conflicting viewpoints. Some points should be pondered.

The importance of the diagnostic context

Polymyalgia rheumatica diagnosis is essentially clinical in the absence of a gold standard diagnostic text. Although studies from institutional databases typically include a large case series, diagnoses of the various diseases are based on coding and not always confirmed by individual medical record reviews. Therefore, registry-based studies may be at the risk of misdiagnosis/misclassification. On the other hand, cohort studies have much less data. Nonetheless, they can have higher diagnostic or classification accuracy, because these patients are carefully chosen to answer a specific research question. Finally, cohort-studies performed on hospitalized patients could favour an inclusion bias because it is uncommon for a patient with typical PMR to be hospitalized [3, 4].

In addition, PMR should always be separated from Horton's disease. Indeed, GCA has a neoplastic risk in itself [5], and assessing these patients together leads to methodological bias [6–8]. Some researchers have proposed that PMR and GCA be viewed as two sides of the same disease. A recent systematic review and meta-analysis of individual patient data concluded that only about a quarter of patients with PMR may have subclinical GCA [9]. This means that about three-quarters of patients with PMR do not have a subclinical GCA.

How long does it take for polymyalgia rheumatica to be considered a paraneoplastic condition?

A review published in 2018 found some evidence of a short-term association (i.e. between 6 and 12 months after diagnosis of PMR) between PMR and cancer. The authors suggested focussing on identifying PMR patients who are most likely to develop a cancer in the short-term [10]. On the other hand, other researchers proposed that the minimum observation time should not be < 24 months [11]. Choosing the duration of the follow-up period for linking PMR to cancer is important in order to avoid arbitrary criteria.

The paraneoplastic meaning of remitting seronegative symmetrical synovitis with pitting oedema syndrome in patients with isolated polymyalgia rheumatica

Remitting seronegative symmetrical synovitis with pitting oedema (RS3PE) is an elderly-onset rheumatic condition, described for the first time by McCarty et al. in 1985, characterized by bilateral and symmetric tenosynovitis of extensor tendons at the wrist and (less frequently) feet. The only case in which the clinical

Address for correspondence:
Ciro Manzo, Rheumatologic Outpatient Clinic, Health District no. 59, viale dei Pini, 1, 80065, Sant'Agnello, Naples, Italy,
e-mail: manzoreumatologo@libero.it

Submitted: 25.10.2022; **Accepted:** 18.11.2022

manifestations are unilateral or asymmetric is when the limb is paretic.

In its benign expression, RS3PE responds quickly to low glucocorticosteroid (GC) dosages, and its relapse is uncommon. Serum levels of the vascular endothelial growth factor (VEGF), a cytokine able to increase vascular dilatation and permeability, are reported to be significantly higher in these patients than in controls. These levels decrease and normalize after treatment with GCs. The importance of VEGF in the neoplastic process could explain the paraneoplastic meaning that some researchers attribute to RS3PE syndrome.

Remitting seronegative symmetrical synovitis with pitting oedema can be a precursor of cancer in elderly patients with rheumatic diseases in up to 20% of cases [12], and no more than 10% of patients with PMR have RS3PE as an accompanying or an initial manifestation [13]. Thus, the presence of this syndrome in patients with PMR is uncommon, but when it does occur, the risk for underlying cancer is high [14].

Fast track approaches for polymyalgia rheumatica patients suspected of cancer

A confirmed positive association between PMR and cancer would imply that increased cancer screening in this population would be beneficial. Simple screening tests such as a chest X-ray, a prostate-specific antigen (PSA) or an ultrasound abdominal assessment may be warranted as part of the diagnostic work-up of PMR.

Fast-track approaches have shown significant reductions in mortality, morbidity, and financial costs for patients in medical specialities. A fast-track clinic (FTC) for PMR patients suspected of cancer might be useful. The absence of prolonged morning stiffness, non-response to GCs and/or absence of suggestive PMR imaging findings and significant unexplained weight loss could identify patients who should be referred to a FTC-PMR.

As already discussed, the feasibility of this working-hypothesis depends mainly on the resources of the national health systems and of the territorial health districts, which are heterogeneously limited. Its utility depends on a close collaboration with the general practitioner who is the first clinician to visit the patient with suspected PMR [15].

Conclusions

The association of PMR with cancer has some points to ponder and clarify. A more rigorous and homogeneous methodological approach is crucial. A fast-track clinic for PMR patients suspected of cancer could be useful.

Engagement and training of primary healthcare providers are highly recommended to accelerate PMR diagnosis and early detection of associated neoplastic sequelae.

The authors declare no conflict of interest.

References

1. Sharma A, Mohammad AJ, Turesson C. Incidence and prevalence of giant cell arteritis and polymyalgia rheumatica: A systematic literature review. Semin Arthritis Rheum 2020; 50: 1040–1048, DOI: 10.1016/j.semarthrit.2020.07.005.
2. Dejaco C, Brouwer E, Mason JC, et al. Giant cell arteritis and polymyalgia rheumatica: current challenges and opportunities. Nat Rev Rheumatol 2017; 13: 578–592, DOI: 10.1038/nrrheum.2017.142.
3. Manzo C, Natale M. Polymyalgia rheumatica and cancer risk: The importance of the diagnostic set. Open Access Rheumtol 2016; 8: 93–95, DOI: 10.2147/OARRR.S116036.
4. Sobrero A, Manzo C, Stimamiglio A. The role of the general practitioner and the out-of-hospital public rheumatologist in the diagnosis and follow-up of patients with polymyalgia rheumatica. Reumatismo 2018; 70: 44–50, DOI: 10.4081/reumatismo.2018.1036.
5. Kermani TA, Schäfer VS, Crowson CS, et al. Malignancy risk in patients with giant cell arteritis: a population – based cohort study. Arthritis Care Res (Hoboken) 2010; 62: 149–154, DOI: 10.1002/acr.20062.
6. Haga H-J, Eide GE, Brun J, et al. Cancer in association with polymyalgia rheumatica and temporal arteritis. J Rheumatol 1993; 20: 1335–1339.
7. Ji J, Liu X, Sundquist K, et al. Cancer risk in patients hospitalized with polymyalgia rheumatica and giant cell arteritis: a follow-up study in Sweden. Rheumatology (Oxford) 2010; 49: 1158–1163, DOI: 10.1093/rheumatology/keq040.
8. Ungprasert P, Sanguankeo A, Upala S, Knight E. Risk of malignancy in patients with giant cell arteritis and polymyalgia rheumatica: A systematic review and meta-analysis. Semin Arthritis Rheum 2014; 44: 366–370, DOI: 10.1016/j.semarthrit.2014.06.004.
9. Hemming AK, Gozzoli D, Werlen L, et al. Subclinical giant cell arteritis in new onset polymyalgia rheumatica: A systematic review and meta-analysis of individual patient data. Semin Arthritis Rheum 2022; 55: 152017, DOI: 10.1016/j.semarthrit.2022.152017.
10. Muller S, Hider S, Helliwell T, et al. The real evidence for polymyalgia rheumatica as a paraneoplastic syndrome. Reumatismo 2018; 70: 23–34, DOI: 10.4081/reumatismo.2018.1031.
11. Bellan M, Boggio E, Sola D, et al. Association between rheumatic diseases and cancer: results from a clinical practice cohort study. Intern Emerg Med 2017; 12: 621–627, DOI: 10.1007/s11739-017-1626-8.
12. Manzo C. The paraneoplastic meaning of R3SPE (Remitting Seronegative Simmetrical Synovitis with Pitting Edema) Syndrome. J Med Oncol Ther 2016; 1: 72–75, DOI: 10.35841/medical-oncology.1.2.72-75.

13. Cantini F, Salvarani C, Olivieri I, et al. Remitting seronegative symmetrical synovitis with pitting oedema (RS3PE) syndrome: a prospective follow up and magnetic resonance imaging study. Ann Rheum Dis 1999; 58: 230–236, DOI: 10.1136/ard.58.4.230.
14. Manzo C, Natale M. Polymyalgia Rheumatica in Association with Remitting Seronegative Sinovitis with Pitting Edema: a Neoplastic Warning. Can Geriatr J 2017; 20: 94–96. DOI: 10.5770/cgj.20.254
15. Hysa E, Ghorbannia A, Emamifar A, et al. Feasibility and usefulness of a fast-track clinic for patients suspected of polymyalgia rheumatica: notes for a work schedule through a narrative review of published literature. Reumatologia 2021; 59: 323–329. DOI: 10.5114/reum.2021.110600.