

If something looks like an apple, is it necessarily an apple? – reflections on so-called “statin-induced polymyalgia rheumatica”

Ciro Manzo

Internal and Geriatric Medicine Department, Rheumatologic Outpatient Clinic Hospital „Mariano Lauro”, Sant’Agnello, Italy

Abstract

The existence of polymyalgia rheumatica (PMR) induced by statins has been hypothesised by some investigators. This review article highlights the fact that there is no evidence it is real. On the contrary, PMR and statin-associated muscle symptoms (SAMS) are two totally different conditions. Shoulder and hip ultrasound (US) examinations can make an important contribution in distinguishing a true case of PMR from a PMR-like illness induced by statins. The possibility that SAMS may worsen the clinical manifestations of a PMR patient should be taken into account in clinical practice, and drug discontinuation should be proposed when deterioration or relapse is not otherwise justifiable.

Key words: polymyalgia rheumatica, statins, methodology, polymyalgia rheumatica-mimicking illness.

Introduction

Polymyalgia rheumatica (PMR) is a common inflammatory rheumatic disease affecting older persons [1, 2]. Bilateral pain, aching and stiffness in the shoulders and pelvic girdle, associated with morning stiffness lasting more than 45 minutes, are typical manifestations. In some patients, an inflammatory pain in the neck is also present [3–5].

To improve the criteria specificity for PMR, the 2012 provisional European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria used, for the first time, findings of shoulder (sub-deltoid bursitis, biceps tenosynovitis and/or gleno-humeral synovitis) and hip (synovitis and/or trochanteric bursitis) ultrasound (US) along with clinical presentations [6]. It worth mentioning that these classification criteria have been designed to discriminate patients with PMR from other mimics of PMR, and are not meant for diagnostic purposes. They supply high sensitivity and specificity [7].

However, even if they still request elevation of the erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) concentrations as mandatory to classify the

patient as PMR, normal ESR and CRP should not be a reason for exclusion for PMR [8–10].

The etiopathogenesis of PMR is still unclear and debated [11–13].

Statin-induced myopathy

Statins or 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors are widely used drugs, able to lower serum cholesterol levels and to reduce the risk of cardiovascular events. Statin-associated muscle disease is by far the most studied and the most common reason for discontinuation of therapy [14]. Statin-induced muscle disease can be classified in two main syndromes:

- statin-induced necrotising inflammatory myopathy (SINIM) [15],
- statin-associated muscle symptoms (SAMS) [16, 17].

SINIM is a rare autoimmune disease related to the presence of anti-HMG CoA reductase antibodies associated with a restricted human leucocyte antigen (HLA) type (DRB1*11:01). It is very rare, and has a reported incidence of less than 2 per million per year. Patients affected

Address for correspondence:

Ciro Manzo, Internal and Geriatric Medicine Department ASL NA 3 sud, Rheumatologic Outpatient Clinic Hospital “Mariano Lauro”, viale dei Pini 1, 80065 Sant’Agnello, Italy, e-mail: cirmanzo@libero.it

Submitted: 4.06.2019; **Accepted:** 18.06.2019

by SINIM develop symmetrical proximal myopathy with grossly elevated creatine kinase (CK). Symptoms persist despite cessation of statin therapy. Muscle biopsy reveals muscle fibre necrosis with minimal endomysial inflammatory infiltrates. Diagnosis is confirmed by the presence of anti-HMG CoA antibodies and characteristic findings on muscle magnetic resonance imaging (MRI).

By contrast, in patients affected by SAMS, proximal myalgia with/without increased CK levels and not raised ESR and CRP concentrations are typically reported. A number of factors including genetic predispositions and drug interactions have been associated with an increased risk of SAMS. For example, interactions due to co-administration of drugs sharing the same cytochrome P450 metabolic pathway may account for up to 60% of SAMS. Drugs such as glucocorticoids, gemfibrozil, protease inhibitors, antipsychotics such as risperidone and immunosuppressives such as cyclosporine, and common food-associated factors such as orange or cranberry juice and excess alcohol consumption have all been implicated. Last but not least important, vitamin D and coenzyme Q₁₀ (CoQ₁₀)/ubiquinone deficiencies can also favour or exacerbate this myopathy [18, 19].

In view of the muscular side effects, some investigators discussed the possibility that PMR could be induced by statins.

Polymyalgia rheumatica and statins. What does the literature say about it?

Until 2012, the association between PMR and statin therapy was anecdotal [20–22]. In all reported patients, ESR and CRP concentrations were raised while CK was normal.

In 2012, de Jong et al. [23] published their analysis using a case/non-case approach in Vigibase (the database of the WHO Uppsala Monitoring Centre), and postulated that the use of statins may be associated with increased occurrence of PMR. However, as the authors themselves underlined, some forms of bias were present, including the lack of information on the therapy of PMR (which is why it was impossible to determine whether clinical improvement was related to statin discontinuation or to treatment with prednisone) and the scarcity of clinical data in the database (which is why the authors were not able to recognize possible diagnostic misclassification).

To our best knowledge, only one new case has been published after this study: in 2015, Onat et al. [24] reported a 53-year-old female suffering from pain in her bilateral shoulders, hips and neck associated with morning stiffness lasting one hour and with proximal weakness, which ensued one week after daily therapy with

40 mg atorvastatin. In this case report, the onset of PMR after statin therapy was just a coincidence.

Polymyalgia rheumatica or polymyalgia rheumatica-like illness?

Polymyalgia rheumatica can mimic several diseases and differential diagnosis is not always easy. Moreover, some patients with PMR-mimicking diseases can have a fast (but transitory) response to systemic glucocorticosteroids (GCs). On the other hand, up to 30% of patients with PMR can fail to have a good response to GCs at 4 weeks. Finally, some patients diagnosed first with PMR may be reclassified as having a different disease during follow-up [25].

Since Bird's criteria published in 1979, a variety of criteria have been proposed with different sensitivity and specificity [26]. Shoulder and hip US examinations can make an important contribution as proposed by EULAR/ACR classification criteria, but their usefulness is counterbalanced by the absence of pathognomonic findings [27, 28]. As highlighted by the EULAR/ACR collaborative group, patients with PMR were more likely to have abnormal ultrasound findings in the shoulder (particularly subdeltoid bursitis and biceps tenosynovitis), and somewhat more likely to have abnormal findings in the hips (particularly trochanteric bursitis and synovitis) than comparison subjects as a group [6]. As in the case report published by Onat et al. [24], US can make a relevant contribution in distinguishing a true PMR from a PMR-like illness induced by statins.

Moreover, as already highlighted, normal ESR and CRP should not be a reason for exclusion for PMR [10], and this may introduce additional diagnostic difficulties in patients suffering from proximal myalgia without increased CK levels and without raised ESR and CRP concentrations, occurring during statin therapy. Nevertheless, also in this particular subset of PMR patients, shoulder and hip US examination can result in settling the issue.

What's in a name? Is that which we call polymyalgia rheumatica the same for all physicians?

As highlighted by other investigators, the risk that PMR could be a magic cauldron in which to put every long-lasting pain localized to scapular and pelvic girdles, quickly responding to GCs, is always just round the corner [29].

When studies are performed using incomplete databases, this risk is very high. In this specific case, we know that the general practitioner (GP) is usually the

first physician who examines the PMR patient [4, 30, 31], that many PMR patients are not referred to rheumatologists [32], that the level of the GP's diagnostic accuracy is often low [33], and that PMR is not a straightforward disease [25].

In this way, what was presented as a strength in the study performed by de Jong et al. [23], that is the evaluation of reports made by physicians, became a potential further bias. This is by no means the first time that studies performed using uncontrolled and incomplete databases generated statistically intriguing findings, without clinical significance.

Conclusions

1. PMR and SAMS are two completely different pathological conditions.
2. PMR involves articular or juxta-articular synovial structures and no muscular involvement is primarily described. SAMS is a myopathy.
3. However, the possibility that SAMS may worsen the clinical manifestations of a PMR patient should be taken into account in clinical practice and discontinuation of a drug should be proposed when a deterioration or relapse is not otherwise justifiable.

The author declares no conflict of interest.

References

1. Raheel S, Shbeeb I, Crowson CA, Matteson EL. Epidemiology of polymyalgia rheumatica 2000-2014 and examination of incidence and survival trends over 45 years: a population-based study. *Arthritis Care Res* 2017; 69: 1282-1285.
2. Cimmino MA, Zaccaria A. Epidemiology of polymyalgia rheumatica. *Clin Exp Rheumatol* 2000; 18: S9-11.
3. Milchert M, Brzosko M. Diagnosis of polymyalgia rheumatica usually means a favourable outcome for your patient. *Indian J Med Res* 2017, 145: 593-600.
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.
5. Muratore F, Pazzola G, Pipitone N, Salvarani C. Recent advances in the diagnosis and treatment of polymyalgia rheumatica. *Expert Rev Clin Immunol* 2016; 12: 1037-1045.
6. Dasgupta B, Cimmino MA, Maradit-Kremers H, et al. 2012 provisional classification criteria for polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative. *Ann Rheum Dis* 2012; 71: 484-492.
7. Muratore F, Salvarani C, Macchioni P. Contribution of the new 2012 EULAR/ACR classification criteria for the diagnosis of polymyalgia rheumatica. *Reumatismo* 2018; 70: 18-22.
8. Manzo C, Milchert M. Polymyalgia rheumatica with normal values of both erythrocyte sedimentation rate and C-reactive protein concentration at the time of diagnosis: a four-point guidance. *Reumatologia* 2018; 56: 1-2.
9. Manzo C. Polymyalgia rheumatica (PMR) with normal values of both erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) concentration at the time of diagnosis in a centenarian man: A case report. *Diseases* 2018; 6: pii: E84.
10. Manzo C, Milchert M, Natale M, Brzosko M. Polymyalgia rheumatica with normal values of both erythrocyte sedimentation rate and C-reactive protein concentration at the time of diagnosis. *Rheumatology (Oxford)* 2019; 5: 921-923.
11. Mackie SL. Polymyalgia rheumatica: pathogenesis and management. *Clin Med (London)* 2013; 13: 398-400.
12. Tshimologo M, Saunders B, Muller S, et al. Patients' views on the causes of their polymyalgia rheumatica: a content analysis of data from the PMR Cohort Study. *BMJ Open* 2017; 7: e014301.
13. Matteson EL, DeJaco C. Polymyalgia rheumatica. *Ann Intern Med* 2017; 166: ITC65-ITC80.
14. Magni P, Macchi C, Morlotti B, et al. Risk identification and possible countermeasures for muscle adverse effects during statin therapy. *Eur J Intern Med* 2015; 26: 82-88.
15. Babu S, Li Y. Statin induced necrotizing autoimmune myopathy. *J Neurol Sci* 2015; 351: 13-17.
16. Maghsoodi N, Wierzbicki AS. Statin myopathy: Over-rated and under-treated? *Curr Opin Cardiol* 2016; 31: 417-425.
17. Alfirevic A, Neely D, Armitage J, et al. Phenotype standardization for statin-induced myotoxicity. *Clin Pharmacol Ther* 2014; 96: 470-476.
18. Banach M, Serban C, Sahebkar A, et al. Effects of coenzyme Q10 on statin-induced myopathy: a meta-analysis of randomized controlled trials. *Mayo Clin Proc* 2015; 90: 24-34.
19. Michalska-Kasiczak M, Sahebkar A, Mikhailidis DP, et al. Analysis of vitamin D levels in patients with and without statin-associated myalgia – A systematic review and meta-analysis of 7 studies with 2420 patients. *Int J Cardiol* 2014; 178: 111-116.
20. Rudski L, Rabinovitch MA, Danoff D. Systemic immune reactions to HMG-CoA reductase inhibitors. report of 4 cases and review of the literature. *Medicine* 1998; 77: 378-383.
21. Goëb V, Guillemant N, Vittecoq O, Le Loët X. Cerivastatin-induced polymyalgia rheumatica-like illness. *Clin Rheumatol* 2004; 23: 179.
22. Kay J, Finn D, Stone J. Case records of the massachusetts general hospital. Case 4–2006. A 79-year-old woman with myalgias, fatigue, and shortness of breath. *N Engl J Med* 2006; 354: 623-630.
23. De Jong HJ, Saldi SRF, Klungel OH, et al. Statin-Associated Polymyalgia Rheumatica. An Analysis Using WHO Global Individual Case Safety Database: A Case/Non-Case Approach. *PLoS One* 2012; 7: e41289.
24. Onat SS, Bicer S, Sahin Z, Özbudak Demir S. Is it statin induced polymyalgia rheumatica or just a coincidence? *Arch Rheumatol* 2015; 30: 261-262.
25. Manzo C, Camellino D. Polymyalgia rheumatica: diagnostic and therapeutic issues of an apparently straightforward disease. *Recenti Prog Med* 2017; 108: 221-231.

26. Bird HA, Leeb BF, Montecucco CM, et al. A comparison of the sensitivity of diagnostic criteria for polymyalgia rheumatica. *Ann Rheum Dis* 2005; 64: 626-629.
27. Mackie SL, Koduri G, Hill CL, et al. Accuracy of musculoskeletal imaging for the diagnosis of polymyalgia rheumatica: systematic review. *RMD Open* 2015; 13: e000100.
28. Falsetti P, Acciai C, Volpe A, et al. Ultrasonography in early assessment of elderly patients with polymyalgic symptoms: a role in predicting diagnostic outcome. *Scand J Rheumatol* 2011; 40: 57-63.
29. Camellino D, Cimmino MA. Are the new ACR/EULAR criteria the ultimate answer for polymyalgia rheumatica classification? *J Rheumatol* 2016; 43: 836-838.
30. Helliwell T, Hider SL, Mallen CD. Polymyalgia rheumatica: diagnosis, prescribing and monitoring in general practice. *Br J Gen Pract* 2013; 63: e361-366.
31. Mathew R, Rashid A. Polymyalgia rheumatica in primary care: managing diagnostic uncertainty. *BMJ* 2015; 351: h5199.
32. Barraclough K, Liddell WG, du Toit J, et al. Polymyalgia rheumatica in primary care: a cohort study of the diagnostic criteria and out-come. *Fam Pract* 2008; 25: 328-333.
33. Manzo C, Natale M, Traini E. Diagnosis of polymyalgia rheumatica in primary health care: favoring and confounding factors – a cohort study. *Reumatologia* 2018; 56: 131-139.