

Polymyalgia rheumatica: an autoinflammatory disorder?

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To cite: Floris A, Piga M, Cauli A, et al. Polymyalgia rheumatica: an autoinflammatory disorder?. *RMD Open* 2018;4:e000694. doi:10.1136/rmdopen-2018-000694

► Prepublication history for this paper is available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/rmdopen-2018-000694>).

Received 4 April 2018
Accepted 8 May 2018



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Polymyalgia rheumatica (PMR) is an elderly onset syndrome characterised by aching and stiffness in the shoulders and the pelvic girdle associated to increased levels of acute phase reactants and rapid response to glucocorticoids.¹ Although the cause of PMR remains unknown, most of the evidence suggest a multifactorial aetiology inducing an immunomediated pathogenesis.^{1,2}

According to the ‘immunological continuum model’ proposed by McGonagle in 2006, all immune-mediated diseases can be conceptualised as predominantly autoinflammatory, predominantly autoimmune or mixed, on the basis of the relative contributions of innate and adaptive immune responses.³ Autoinflammatory diseases (AIDs) are characterised by tissue inflammation mainly due to aberrant activation of innate immune system without autoantibodies production and autoreactive T lymphocyte activation. In contrast, autoimmune diseases (ADs) are typically depicted by an abnormal activation of the adaptive immune system.⁴ However, the emerging understanding of the close linkage between innate and adaptive immunity led to consider the rare monogenic AIDs and ADs as the two opposite ends into a continuum of immune-mediated disorders, where middle entities are recognised (figure 1).³

In the view of this background, we tried to envisage the most suitable place for PMR into the spectrum of the autoinflammatory/autoimmune disorders by reviewing and interpreting current evidence.

Clear indication for a prevalent autoinflammatory background of PMR is related to the disease onset and course. Actually, starting of symptoms is generally over a few days or overnight in PMR,¹ as well as in inflammatory periodic-recurring occurrence of AIDs,⁵ but in contrast to classic polygenic ADs where a subacute onset is frequently recorded

(figure 2A).⁶ Further, after low-dose glucocorticoid therapy initiation, patients with PMR experience a rapid improvement of symptoms, generally within 24–72 hours, and more than 40% of them achieve complete response within 3 weeks.¹ Similarly, in rare monogenic AIDs, a rapid remission of symptoms and significant reduction in frequency of inflammatory attacks is rapidly achieved with specific treatment, such as colchicine in familial Mediterranean fever (FMF) and interleukin-1 β (IL-1 β) blockade in cryopyrin-associated periodic syndrome.⁷ Conversely, a chronic or relapsing-remitting course, with a minimal residual disease activity and progressive damage accrual, is frequently recorded in ADs (figure 2B).⁸

Age of onset and gender distribution are inconclusive in discriminating the prevalent autoinflammatory or autoimmune nature of PMR (figure 2C). Indeed, both in ADs and AIDs elderly onset is rare, and the main determinant of the onset age is the monogenic (childhood) or polygenic (adulthood) nature of the disease.^{4,9} Further, the preferential involvement of woman in PMR (female to male ratio=2:1) seems related to a different and currently unknown mechanism than the arise in oestrogen production reported as one of the main determinants of the female prevalence in typical ADs, such as systemic lupus erythematosus (SLE) (female to male ratio=9:1).¹⁹

Laboratory findings lean towards a predominant role of innate immune response in PMR. Indeed, a remarkable increase of inflammatory markers is one of the most consistent features in patients with both PMR and AIDs, so that it is included into the diagnostic criteria and monitoring parameters for both conditions.^{1,7} Increase of acute phase reactants can also occur in ADs, but with lower frequency and diagnostic accuracy (figure 2D).⁴ Further, autoantibodies carrying

Autoinflammatory diseases (AIDs)		Mixed	Autoimmune diseases (ADs)	
Monogenic	Polygenic	Polygenic	Polygenic	Monogenic
FMF	Crohn disease	Ankylosing spondylitis	SLE	APS
CAPS	Gout	Psoriatic arthritis	SS	IPEX
HIDS	Behçet disease		SSc	ALPS
TRAPS	sJIA		PM/DM	
			MCTD	

In the chromatic bar, red (left side), yellow (central) and green (right side) represent the continuum of autoinflammatory, mixed and autoimmune diseases. FMF: Familial Mediterranean fever; CAPS: cryopyrin-associated periodic syndrome; HIDS: hyper-immunoglobulinemia D syndrome; TRAPS: TNF receptor-associated periodic syndrome; sJIA: systemic juvenile idiopathic arthritis; SLE: systemic lupus erythematosus; SSc: systemic sclerosis; SS: Sjögren's syndrome; PM/DM: polymyositis and dermatomyositis; MCTD: mixed connective tissue diseases; APS: autoimmune polyendocrinopathy syndrome; IPEX: immune-dysregulation polyendocrinopathy enteropathy X-linked syndrome; ALPS: autoimmune lymphoproliferative syndrome.

Figure 1 Simplified classification of immune-mediated disease by McGonagle and McDermott.³

a significant pathogenic and/or diagnostic role have not been identified in PMR, as well as in AIDs,⁴ whereas they are frequently associated to prototypical ADs (eg, anti-double-stranded DNA in SLE, anti-citrullinated peptide in rheumatoid arthritis (RA)) (figure 2E).^{4,10} Noteworthy, lack of pathogenetic autoantibodies is typically recorded in other immune-mediated diseases, such as the major histocompatibility complex class I (MHC-I)-pathies (eg, ankylosing spondylitis, psoriatic arthritis) that are reported as prototypical mixed autoinflammatory/autoimmune disorders in the immunological continuum.³

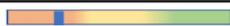
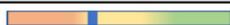
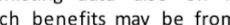
Similar to AIDs and in contrast to what is reported for typical ADs, not significant overlap has been identified between PMR and other immunological disorders, excepting for giant cell arteritis (GCA).¹¹ However, it is still unclear whether GCA represents a separate condition from PMR or a potential expression of the same disease (figure 2).^{3,12} Further, a mixed contribution of innate and adaptive immunity, supported by the bringing function of Th17 cells, has been recognised in the GCA.¹

Despite the widely incomplete knowledge on pathogenesis of PMR, some suggestions for a predominant autoinflammatory nature of the disease arise from the genetic background and cytokine profile. Indeed, a clear association between human leukocyte antigen (HLA) class II alleles (especially HLA-DRB1*0401) and isolated PMR has not been definitely demonstrated due to conflicting data from different populations.¹ On the other hand, HLA class II alleles have been found to associate with GCA susceptibility and GCA with PMR symptoms, as well as in most of ADs (figure 2G).^{13–15} Polymorphisms of additional genes involved in initiating and regulating inflammatory response, such as intercellular adhesion molecule-1, tumour necrosis factor (TNF), interleukin 6 (IL-6) and interleukin 1 (IL-1) receptor antagonist (IL-1RN) have also been identified as possible susceptibility factors for PMR.¹⁶ Interestingly, Alvarez-Rodriguez reported that the IL-1RN*2 polymorphism in a homozygous state associated to higher susceptibility to PMR when compared with healthy controls and GCA, as well as to elderly onset RA (EORA) when compared with young-onset RA.¹⁵

Regarding the cytokine profile, evidence of a IL-6 central pathophysiological role in PMR has been provided. Remarkably, among rheumatic diseases, the highest serum levels of IL-6 were found in patients affected by PMR and GCA¹⁷ as well as in EORA.¹⁸ The latter presents some not canonical features compared with traditional ADs (eg, lower prevalence of autoantibodies, reduced prevalence in females, less straight association with HLA-II) and might be part of an autoinflammatory–autoimmune mixed subtype of RA.¹⁹ Further, in contrast to several ADs, increased levels of serum interferon- γ (IFN- γ) were not found in PMR. Moreover, IFN- γ was observed in the temporal artery biopsy (TAB) specimens of GCA patients, while it was not seen in TAB of patients with isolated PMR, suggesting a key role of this cytokine in the progression to overt arteritis.²⁰ Finally, increased level of circulating type I IFN has not been reported neither on PMR and GCA²¹ and no data are currently available on type I IFN signature, which is considered an hallmark of several ADs (figure 2H).

Further pathobiological findings supporting the key role of innate immunity in PMR pathogenesis are represented by the increased expression of toll-like receptor (TLR)-7 and TLR-9 in peripheral blood monocyte cells and the emerging involvement of Th17 cells.²²

To date, glucocorticoids remain the cornerstone of treatment for PMR, whereas poor evidence is available on the effectiveness of traditional immunosuppressants. Methotrexate (MTX) is the most used glucocorticoid-sparing agent in PMR, although randomised controlled trials data on relapse rate and cumulative glucocorticoid dose reduction are conflicting.²³ Potential benefit of MTX may be related to antiinflammatory effects, resulting from reduced monocyte cell activation, decreased IL-1 and IL-6 secretion, as well as from inhibition of cyclo-oxygenases synthesis, neutrophil chemotaxis and adhesion molecules expression.²⁴ Traditional immunosuppressants are generally not used in AIDs because of the poor effectiveness in the management of attacks and prevention of relapse.^{7,25} Conversely, traditional immunosuppressants are the first-line treatment in most of ADs, while glucocorticoids can be associated

	In typical AIDs	In PMR	In typical ADs
a. Disease onset	Acute / hyper-acute onset of recurring inflammatory attacks.	 Onset of symptoms is generally over a few days or overnight.	Frequent subacute onset in most of ADs.
b. Disease course	Rapid remission is frequently achieved with specific treatment, such as colchicine in FMF or anti-IL1 β blockade in CAPS.	 Rapid improvement of symptoms, generally within 24–72 hours, with complete response achieved in $\geq 40\%$ within 3 weeks.	Frequent chronic or relapsing-remitting course, with minimal residual disease activity and progressive damage accrual.
c. Onset age and gender distribution	Monogenic in infancy; polygenic usually in the adulthood, without gender prevalence. Rare in elderly.	 Exclusively in people >50 years (peak incidence >65 yrs). Two third of patients are woman.	Monogenic in infancy; polygenic more frequent in woman in childbearing age. Rare in elderly.
d. Acute phase reactants	Remarkable increase of acute phase reactants in most of AIDs.	 Remarkable increase of acute phase reactants great majority of patients.	Increase also in several ADs, but with lower diagnostic accuracy than AIDs.
e. Autoantibodies	No autoantibodies with significant diagnostic and/or pathogenic role.	 No autoantibodies with significant diagnostic and/or pathogenic role.	Frequent presence of autoantibodies with significant pathogenic and diagnostic role (e.g. anti-dsDNA and anti-Sm in SLE).
f. Overlap with other immunological disease	No significant overlap with other immune-mediated diseases.	 No significant overlap has been identified between PMR and other immune-mediated diseases, excepting for GCA.	ADs frequently overlap with each other.
g. Genetic background	Not associated to HLA class II.	 Conflicting data on association to HLA-II alleles. Polymorphisms of genes involved in the initiation and regulation of inflammatory (e.g. ICAM-1, TNF, IL-1 β , RANTES, IL-6)	HLA region (especially class II) is among the strongest genetic risk factors for most of ADs.
h. Cytokine profile	Pivotal role of IL-1 β . Increased levels of IL-6 in several AIDs, such as FMF, HIDS, TRAPS, Behçet. No evidences of IFNs involvement.	 Pivotal role of IL-6. Increased expression of IL-1 β in interstitial muscle tissue. No increase level of type I e II IFNs.	A common cytokine not identifies. Highest circulating IL-6 in elderly onset RA. A significant activation IFN genes in SLE, DM, PM, RA, SS.
i. Traditional immunosuppressants (tIS)	tIS generally not used because the poor evidence of their effectiveness in management of attacks and prevention of relapses.	 GC cornerstone of therapy. Conflicting data on effectiveness of tIS as steroid-sparing agents. Conflicting data also on MTX, which benefits may be from its autoinflammatory effect.	tIS are the cornerstone in treatment of the majority of ADs, having a disease-modifying effects. GC are considered as adjuvants.
j. Biological immunosuppressants (bIS)	Anti-IL6R and anti-IL-1 β effective in treatment of several mono- and polygenic AIDs. Anti-TNF used in several AIDs, but not as a first line treatment.	 Promising data on use of anti-IL6R. Poor data on anti-IL-1 β . Anti-TNF ineffective and potentially harmful. PMR not reported as paradoxical effect of anti-TNF.	Anti-IL6R and anti-IL-1 β approved for treatment of RA. Use of anti-TNF in several ADs limited by the risk of paradoxical induction immunological disorders.

Features of prototypical autoinflammatory (AIDs) and autoimmune diseases (ADs) are reported in the red (left side) and green (right side) column, respectively; in the central chromatic bar the position of the vertical line represents the affinity level of polymyalgia rheumatica (PMR) with AIDs or ADs, in regards of the disease aspect examined in the respective row.

FMF: familial Mediterranean fever; CAPS: cryopyrin-associated periodic syndrome; SLE: systemic lupus erythematosus; GCA: giant cell arteritis; PM: polymyositis; DM: dermatomyositis; RA: rheumatoid arthritis; SS: Sjögren's syndrome; IL-1 β : interleukin-1 β ; IL-6: interleukin-6; ICAM-1: intercellular adhesion molecule-1; TNF: tumor necrosis factor; RANTES: regulated on activation, normal T cell expressed and secreted; IFN: interferon; tIS: traditional immunosuppressants; bIS: biological immunosuppressants; MTX: methotrexate

Figure 2 Summary of our interpretation of scientific data on polymyalgia rheumatica, in the view of its classification in the spectrum of immune-mediated diseases.

as adjuvant therapy, especially in the induction phase of the treatment (figure 2I).²⁶

Experience from patients with PMR symptoms in GCA and data from an open-label uncontrolled study on 20 subjects with isolated PMR suggest anti-IL-6R therapy as an effective option in reducing Disease Activity Score and reducing cumulative exposition to glucocorticoids (glucocorticoid-sparing effect at 24 weeks is 70.2%).²⁷ Anti-IL-6R also showed promising results in several AIDs, such as systemic juvenile idiopathic arthritis, Behçet disease, FMF and TNF receptor-associated periodic syndrome.²⁸ Most of current data on anti-TNF treatment suggest it is ineffective, expensive and potentially harmful in patients with PMR.¹ Positive results in terms of effectiveness were detected for connective tissue diseases and other ADs, but its use is limited by the observation of several cases of anti-TNF-induced autoimmune disorders.²⁹ Interestingly, PMR is not reported among the immune-mediated paradoxical effect of anti-TNF (figure 2J). Data on anti-IL-1 β are limited to a single blind study, where canakinumab was administered to three patients with new-onset PMR, with not conclusive results in terms of effectiveness.³⁰ Therefore, further data from large trial on anti-IL-1 β in PMR would be warranted.

In summary, despite the incomplete knowledge of PMR pathophysiology and the lack of validate discriminative criteria for polygenic AIDs, current evidence suggests that PMR does not easily fit into any of the two pure ends in the spectrum of the immune-mediated disorders, but a greater affinity for AIDs seems to emerge.

In our opinion, this interpretation of the available scientific data might represent an insight with a significant practical implication. Indeed, among the unmet needs in PMR, there is the availability of effective and safety therapeutic options for patients not adequately responsive or requiring longer exposition to glucocorticoids or with an unfavourable risk profile of steroid-related adverse effects. In this view, the recognition of predominantly autoinflammatory nature of PMR should address future research aimed to develop targeted therapies.

Contributors AM: conceived of the present idea. AF and MP: equally contributed to perform the literature review and draft the manuscript. All authors contributed to the interpretation of the recorded evidence. AC, CS and AM: critically reviewed the manuscript. All Authors approved the final version.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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