Review paper

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Infective agents and polymyalgia rheumatica: key discussion points emerging from a narrative review of published literature

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Abstract

Introduction: The aetiology of polymyalgia rheumatica (PMR) is unknown. Recently, reports on cases of PMR following the coronavirus disease 2019 (COVID-19) have revived the role of infection as an aetiological or triggering factor. It is estimated that patients with PMR have manifestations of giant cell arteritis (GCA) in < 20% of cases. To date, little is known on the potential role of infectious agents in facilitating this association. Given this background, we performed a review of published literature. Our first aim was to review and discuss the relationship between PMR and infective agents. Secondly, we compared data of PMR-only patients with PMR and overlapping GCA to seek any commonalities or differences regarding the type of infectious agent in these two subgroups.

Material and methods: We performed a non-systematic literature search on Embase and Medline (COVID interface) with the following search terms: "polymyalgia rheumatica" AND "infections" OR "infectious agents", both MESH headings and free-text (in each language they were written). Each paper's reference list was scanned for additional publications meeting this study's aim. When papers reported data partially presented in previous articles, we referred to the most recent published data. Abstracts submitted at conferences or from non-peer-reviewed sources were not included. Polymyalgia rheumatica following vaccinations was an additional exclusion criterion.

Results: Several infectious agents have been held responsible for PMR. However, no definite causal link has been identified so far. According to our review, the search for a specific infectious agent, however intriguing, appears to be stagnating. Genetic background and epigenetic regulation probably play a key role. However, topical studies are lacking. Polymyalgia rheumatica as an adverse event following immunization should be kept methodologically distinct from PMR following an acute infection, as the adjuvants in the vaccine can make a significant difference.

Conclusions: Finally, some infectious agents are able to replicate in human arteries or have an endothelium tropism. Whilst these can theoretically trigger GCA, their role in isolated PMR seems minimal.

Key words: polymyalgia rheumatica, narrative review, infectious agents.

Introduction

Polymyalgia rheumatica (PMR) is one of the most common inflammatory rheumatic diseases among older people, especially in the 70 to 80 age group [1–3]. At present, no specific laboratory tests are available, and PMR diagnosis is based on recognition of a clinical syndrome. Typically, PMR patients complain of a sudden-onset bilateral pain in shoulder and pelvic girdles, associated with morning stiffness lasting more than 45 min. Neck ache may also be present. Additionally, some patients may have systemic manifestations such as fever or low-grade fever, general malaise, and weight loss [4–7]. As similar clinical signs might indicate other conditions or diseases, differentiating between PMR and what looks like PMR (so-called "PMR-like conditions" or "PMR

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mimickers") – including infections – may be a challenge in everyday clinical practice [8–10]. Inflammatory markers (erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP] concentrations, primarily) are usually raised before starting therapy with glucocorticosteroids (GCs). However, some PMR patients have ESR and CRP values in their normal ranges at the time of diagnosis [11–14].

The aetiology of PMR is still being explored and debated. Recently, a report on a case of PMR following the coronavirus disease 2019 (COVID-19) has revived the role of infection as an aetiological or triggering factor [15].

Finally, PMR may be associated with giant cell arteritis (GCA), a granulomatous non-infectious large vessel vasculitis. It is estimated that patients with PMR show symptoms of GCA in < 20% of cases [16, 17]. What is the role of infectious agents in patients with isolated PMR when compared with patients with overlapping GCA? In other words, do infections facilitate this association or not?

Given this background, we performed a review of published literature. Our first aim was to review and discuss the relationship between PMR and infective agents. Secondly, we compared data of PMR-only patients with PMR and overlapping GCA to seek commonalities or differences, if any, about the type of the infectious agent in these two subgroups.

Material and methods

We performed a non-systematic (PRISMA protocol not followed) literature search on Embase and Medline (OVID interface) with the following search terms: polymyalgia rheumatica AND infections OR infectious agents – both MESH headings and free text (in each language they were written). Each paper's reference list was scanned for additional publications meeting this study's aim. When papers reported data partially presented in previous articles, we referred to the most recent published data. Abstracts submitted at conferences or from non-peer-reviewed sources were not included. PMR following vaccinations was an additional exclusion criterion.

Results

Polymyalgia rheumatica and Lyme disease

In the 1980s and in the 1990s, some clinicians investigated the relationship between PMR and *Borrelia burgdorferi* infection/Lyme disease [18–20]. In particular, Schwartzberg et al. reported in 1995 the case of a 66-year-old white woman suffering from acute onset of severe neck, bilateral shoulder and upper arm pain without erythema migrans rash. These findings were associated with elevation of ESR and liver enzymes, and positive immunoglobulin (Ig) A and G serology (ELISA). Initial therapy with prednisone 15 mg/day was ineffective; the patient made a full recovery after treatment with antibiotics (ceftriaxone 2 g/day for 2 months; then, azithromycin 500 mg/day for 3 months). For Schwartzberg et al. [20] this was the first documented report of acute Lyme disease presenting as polymyalgic syndrome, without erythema migrans. Usually, Lyme disease migrates from the skin to the joints.

In accordance with recommendations of the Centers for Disease Control and Prevention, diagnostic levels of antibody to *B. burgdorferi* at a later stage of disease must be detected by a two-test approach: firstly, a quantitative screening test for serum antibodies to *B. burgdorferi* using an ELISA test; then, a Western blot (WB) must be carried out, and an IgM WB can be considered positive only if at least 2 bands out of three are present (23, 39, or 41 kDa) [21–23]. Only WB band 41 was positive in Schwartzberg's patient. Therefore, in the absence of erythema migrans rash, the authors' Lyme disease diagnosis, whilst highly probable, was not certain. On the other hand, the ineffectiveness of prednisone and the full recovery in this patient after long-term therapy with antibiotics deserve to be highlighted as *ex-adiuvantibus* elements [20].

In all other retrieved case reports, a polymyalgic presentation followed erythema migrans rash and tick bite, but Lyme serology was incomplete or questionable. For example, in some patients, specific IgG antibodies are still present after treatment with antibiotics, although the spirochete seems to be cleared from the body [24]. Additionally, cross-reactivity with viral infections or autoimmune diseases is far from uncommon in everyday clinical practice. Finally, the IgG titre against *B. burgdorferi* was not significantly different (12.5 % vs. 10.3%) in a comparative study on patients with PMR and patients without PMR performed in an Italian region where Lyme disease is endemic [18]. Therefore, concluding that *B. burgdorferi* is a causal or trigger factor for PMR cannot only be based on the presence of specific IgG, as some clinicians would argue.

Finally, both PMR and Lyme disease can be associated with the DR4 locus of the major histocompatibility complex (MHC), and this genetic background could further explain the similarities between these two diseases [18, 25].

Nowadays, this research avenue seems completely disregarded. However, Lyme disease should always be considered in the differential diagnosis of PMR in endemic areas, particularly due to the potentially deleterious effects of GCs in patients with Lyme disease [19].

Polymyalgia rheumatica and viruses

Our literature search shows that for most cases of PMR following infections, the offending infectious agent was a virus.

Specifically, the possibility that a virus may contribute to the aetiology of PMR has been discussed by several researchers on the basis of an increased prevalence of antibodies to some viruses in patients with PMR. Numerous viruses have been suspected: influenza B virus, parvovirus b19, SARS-CoV-2, enterovirus, adenovirus and respiratory syncytial virus, Epstein-Barr virus, hepatitis B virus, human immunodeficiency virus, human parainfluenza type 1 virus, among others [26–28]. However, due to weak data, there is no agreement over an active role of viruses as a PMR trigger. Data are mostly drawn from small series, and potential bias is acknowledged by the authors in several reports (i.e., a geographical or a reverse causation bias).

Perhaps worthy of more attention is PMR following an acute viral infection. In 2015, Japanese clinicians reported on an 85-year-old woman who developed PMR a month after having influenza B. As the authors pointed out, this chronological immediacy suggested (but did not prove) influenza B virus as a possible cause of PMR [29].

More recently, several reports have highlighted a diagnosis of PMR within a few weeks of SARS-CoV-2 infection. In a US retrospective cohort study based on the TriNetX U.S. Collaborative Network (a dataset containing de-identified electronic health records of > 250 million participants from more than 120 healthcare organizations), the COVID-19 cohort exhibited significantly higher risks of PMR (with an adjusted hazard ratio of 2.90) vs. the non-COVID-19 cohort [30]. A South Korea study compared the incidence of some inflammatory rheumatic diseases during the COVID-19 pandemic (from a countrywide healthcare claims database) with data from the previous 4 years: the annual incidence of PMR (RR = 1.075; 95% CI: 0.928–1.239) exhibited an increasing trend, yet without reaching statistical significance [31]. An Italian study found that 28 out of 112 patients in a post-COVID 19 cohort were diagnosed with PMR. None of these patients had clinical features suggestive for GCA on the basis of clinical judgement. Two cases of PMR were identified in a case series of patients diagnosed with COVID-19 a few weeks prior [32]. The possibility that SARS-CoV-2 can trigger relapse of PMR has also been reported [33].

Finally, the possibility that chikungunya virus (CHIKV) can cause PMR (or a PMR-like syndrome) is still debated. Chikungunya virus is a mosquito-borne alphavirus isolated for the first time in Tanzania, known to induce various musculoskeletal manifestations. The name "chikungunya" was firstly used by the local Tanzanian Makonde people and can be translated as "disease that bends up the joints" [34]. Some of these patients may suffer from a long-lasting arthritis akin to rheumatoid arthritis [35, 36]. Recently, cases of PMR have been reported in a cohort of U.S. Military Health System beneficiaries [37]. However, the median age was 42 years, and no diagnostic or classification criterion for PMR was specified. Consequently, further research is needed to clarify the potential relationship between PMR and CHIKV.

Polymyalgia rheumatica and bacteria: subacute bacterial endocarditis and Whipple's disease

The first description of a possible association of PMR and subacute bacterial endocarditis (SBE) dates back to 1976, when Gretillat et al. [38] reported on bacterial endocarditis revealed by rhizomelic pseudopolyarthritis. This association has been confirmed [39–42]. Specifically, other French clinicians reported 3 cases of SBE mimicking PMR/GCA in two cases and isolated PMR in one. These patients had an asymmetrical involvement of scapular and pelvic girdles, which is not common in true PMR [39]. Severe malaise (considered to be disproportionate to the other findings), low-grade fever and lack of response to > 15 mg/day prednisone were warning manifestations in a 73-year-old man, who was initially diagnosed with typical PMR and overlapping GCA [41]. Blood cultures and trans-thoracic echocardiographies should always be checked in patients with polymyalgic manifestations, especially in patients with previously known valvular heart diseases, in order to rule out SBE [42].

Whipple's disease is a rare infection caused by an actinobacterium (*Tropheryma whipplei*). Especially in an early phase (< 6 years) almost all patients suffer from the articulo-muscular involvement which is akin to manifestations of common rheumatic disorders [43]. Notably, polymyalgic manifestations can be present and they often delay Whipple's diagnosis [44].

Peaks of polymyalgia rheumatica and epidemics of infections

A Danish study found correlations between incidence peak of PMR and 2 epidemics of *Mycoplasma pneumoniae* infection. The authors discussed the possibility that this correlation could indicate a role of this bacterium in the causation of PMR [45].

Other studies have failed to find concurrence between incidence peaks of PMR and epidemics of infectious diseases [46–49].

Infectious agents in patients with isolated polymyalgia rheumatica and in patients with polymyalgia rheumatica/giant cell arteritis

Our searches retrieved a small number of articles about infections in which patients with PMR were clearly

distinguished from those with overlapping GCA. French researchers conducted between 1991 and 1995 a prospective, multicentre case-control study on coexisting cases of PMR and GCA, based on the IgG and IgM seroprevalence for viruses known to induce multinucleated giant cells in human pathology. They found no statistically significant difference when the PMR subgroup was compared to a population control (32 vs. 20.9 %; $p = 0.054$) [28]. In 2018, a Danish population case-control study found an adjusted odds ratio (OR) higher for the PMR + GCA subgroup than an isolated PMR subgroup, both when hospital-treated infections (2.07 vs. 1.41) and when all community-based infective prescriptions (1.62 vs. 1.35) (in both cases including only events occurring in the year prior to the index date) were assessed [45].

The role of genetics and epigenetics

The significance of association with the DR4 locus of the MHC in patients with PMR and some infectious diseases has been proposed as a working hypothesis [18, 25]. However, our search yielded no published findings on this.

Discussion

Whilst several infectious agents have been held responsible for PMR, infections may have polymyalgic manifestations. Therefore, infections must always be excluded before diagnosis of PMR, especially in patients with fever or low-grade fever, and/or organ-specific manifestations [50–54]. Also, temporal association between infection and PMR alone does not imply causality, and may merely represent a coincidental association. Finally, infections occurring close to the diagnosis of PMR might be misclassified, thus resulting in a reverse causation bias.

Some key discussion points emerged from our review.

Firstly, it has been discussed that the biological mechanisms linking PMR to vaccination as adverse events following immunization (AEFI) may be similar to those of PMR following acute viral infection. We chose to exclude PMR as an AEFI in our literature search. Indeed, some open questions need answers in order to achieve a better understanding of the relationship between vaccines and PMR (or PMR-like syndromes, more often). For example, it is still being debated whether post-vaccination PMR is caused by virus antigens or adjuvants in the vaccine (thus being an expression of an autoimmune/inflammatory syndrome induced by adjuvant [ASIA]) [55–60]. This question has been stressed by the recent COVID-19 vaccination campaign [61]. With regard to the nucleoside-modified mRNA vaccines against COVID-19, mRNA is encapsulated in lipid nanoparticles containing ionizable lipids (iLNPs). The ionizable lipid is a component crucial for the adjuvant effect, and this effect is significantly powerful. Indeed, empty LNPs (without the ionizable lipids) do not induce strong antibody responses [62, 63]. To date, whether and how iLNPs may trigger an ASIA syndrome following COVID-19 vaccination is still being discussed.

In addition, over-reporting of PMR following vaccination seemed more than likely in some databases typically compiled by consumers, non-health professionals and anonymous imputers [64–67].

These reflections could explain the significant discrepancy between the number of cases of PMR following COVID-19 vaccination and the number of PMR cases following SARS-CoV-2 infection reported in the published literature: PMR cases during or immediately after SARS-CoV-2 infection were much less frequently reported than PMR cases after COVID-19 vaccination. In a large Italian multicentric observational cohort study, the post-COVID-19 cohort had a higher percentage of patients classified as having inflammatory joint diseases (peripheral spondyloarthritis was the most frequent final diagnosis) (52.5% vs. 37.2%, $p = 0.013$) while the post-vaccine cohort had a higher prevalence of patients classified with isolated PMR (33.1% vs. 21.3%, $p = 0.032$). In both cohorts, the time of onset of the rheumatic manifestations was stated to be within 4 weeks [68]. Only one of the 4 patients with PMR reported by Hsu et al. had a similarly rapid onset time. Diagnosis of PMR was instead made > 100 days after negativization of the SARS-CoV-2 PCR test in the other 3 patients, thus suggesting that this connection could be coincidental [69].

Another discussion focus is on aging as a bridge between infectious disease and PMR. As already pointed out, PMR is a rheumatic inflammatory disease of the elderly. Immunosenescence, the progressive decline in the immune system functions associated with aging, can favour – among other consequences – an increase of incidence and severity of infections [70, 71]. Immunosenescence may be a link between PMR and infections, but also a channel for all other elderly-onset inflammatory rheumatic diseases (EOIRDs). If so, why would it favour PMR over other EOIRDs? [72].

Furthermore, we must keep in mind that the probability of an infection increases not only according to age (i.e. older = greater risk), but it is also closely related to concomitant chronic diseases. This means that aging alone does not explain increased susceptibility to infections. Therefore, an elderly but healthy person may be more protected from infections than a younger person in poor health [73].

Finally, according to some investigators, immunosenescence primarily involves the adaptive immune system, and should be kept separate from the so-called "inflam-

maging" that primarily involves innate immune system [74–76]. The role of the adaptive and innate immune system in PMR pathogenesis has been recently revisited in a systematic review which did not rule out the hypothesis that PMR can be an autoimmune disease [77].

What is certain is that reliable data on connections between immunosenescence/inflammaging and specific infectious diseases are not yet available.

A third discussion point is whether incidence peaks of PMR and epidemics of infectious diseases may be synchronous. For example, seasonal peaks in the onset of PMR and infections should be compared. Published research on this connection has so far produced extremely mixed results. As most studies are retrospective, it is difficult to establish a causal relationship between onset of PMR manifestations and infection. Then again, a recent systematic review and meta-analysis concluded that seasonality does not affect the onset of PMR. Specifically, the meta-analysis found a pooled incidence rate ratio (IRR) where onset variations between warm and cold seasons are not significant [78].

Finally, the co-occurrence of GCA in patients with PMR deserves a separate discussion. The possibility that GCA and PMR are concurrent diseases rather than a continuum or different faces of the same disease (so-called "GCA-PMR spectrum disease") has recently been revisited [79]. Little is known about the potential role of infections in facilitating this association. Therefore, we decided to compare isolated PMR with PMR/GCA reports in published literature in order to find any common findings or differences with respect to the role of infectious agents.

We found only two studies in which data on the PMR subgroup were clearly separated from data on the PMR + GCA subgroup (including all patients with a diagnosis of both PMR and GCA). In one of these, the authors found an adjusted OR higher for the PMR + GCA subgroup when compared with the isolated PMR subgroup [40]. Otherwise, the main trend in the literature is to consider PMR and GCA as one disease [80, 81], thus merging data for the two subgroups.

This approach could favour methodological bias, because some viruses have an endothelium tropism, hence potentially playing a role in the causation of GCA. This role is minimal for patients with isolated PMR, and this should be taken into account when assessing the role of individual infectious agents.

For instance, let us consider the case of varicella zoster virus (VZV) and of SARS-CoV-2. A recent meta-analysis detected a significant positive association between prior herpes zoster (HZ) infection and onset of GCA. This association was also found in patients with GCA associated with PMR, but it was not found in patients with isolated PMR [40]. Varicella zoster virus is able to replicate in human arteries, and its role in causing or triggering GCA has been discussed [82–84] and recently revaluated [85]. Much less clear is the relationship between VZV and PMR.

The SARS-CoV-2 virus is also known to have an endothelial tropism. An English population-level retrospective study concluded that there had been a 118% increase in GCA cases in the first wave of the COVID-19 pandemic; that the incidence rate of GCA in the pandemic years of 2020 and 2021 had been double that in the non-pandemic years of 2015–2019; and finally that there was a significant association between COVID-19 and GCA diagnosis with a delay of 40–45 days [86]. A similar increase was observed in a French cohort [87]. However, GCA and COVID-19 may have overlapping features, and some researchers proposed a checklist to avoid diagnostic confusion. Therefore, clinicians should question whether GCA is present rather than a COVID-19 symptom akin to GCA [88]. To the best of our knowledge, diagnosis for cases of PMR and COVID-19 is not as opaque.

Conclusions

Several infectious agents have been held responsible for PMR. However, no clear-cut association has yet been identified. Furthermore, infections may have polymyalgic manifestations, and infections occurring close to the diagnosis of PMR might be misclassified. However intriguing, the search for a specific infectious agent is ridden with difficulties, and seems to be getting nowhere.

Genetic background and epigenetic regulation probably play a key role. However, considering the dearth of targeted studies, as of today it is not possible to go beyond more or less fascinating speculations.

Polymyalgia rheumatica as an AEFI should be kept methodologically distinct from PMR following an acute infection, as the adjuvants in the vaccine can make a significant difference.

Finally, some infectious agents have an endothelium tropism, and they theoretically can trigger GCA. The role of these same agents seems minimal in isolated PMR. Whether this can support the statement that PMR and GCA are two potentially concurrent/overlapping diseases rather than a continuum (or two sides of a coin) is a question requiring further *ad hoc* studies.

Disclosures

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Data availability: The data that support the findings of this study are available on request from the corresponding author (C.M.).

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