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A History of Polymyalgia Rheumatica: A Narrative Review

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Abstract

Polymyalgia rheumatica (PMR) is characterised by stiffness and pain in the shoulders, hips, and neck and presents most commonly in the eighth decade. It can coexist with giant cell arteritis and the two diseases may share some pathophysiological mechanisms. This narrative review considers present-day ideas about PMR in a historical context, from the first names and descriptions of this disease entity, via successive generations of classification criteria sets, and finally to implications for clinical diagnosis. The characteristic distribution of musculoskeletal inflammation in PMR, and its relationship to vasculitic and synovitic diseases, have framed the way that PMR is described, classified, diagnosed and treated. A response to glucocorticoids is not specific to PMR and so it is important for rheumatologists to support general practitioners in making a definite diagnosis. Multi-stakeholder collaboration will improve current pathways for fast, accurate diagnosis and safe and effective treatment.

Keywords

Polymyalgia Rheumatica

History of Medicine

Attitude of Health Personnel

Giant cell arteritis

Classification criteria

Introduction

Polymyalgia rheumatica (PMR) is one of the commonest rheumatic diseases with an annual incidence of 112.6/100,000 population over 50 in one Northern European population. (1) Like most rheumatic diseases the diagnosis of PMR is based on pattern recognition rather than by defining a cut-point along a unidimensional linear scale. PMR is said to present with a syndrome of bilateral, symmetrical shoulder girdle pain and stiffness, yet a similar syndrome may be seen in a multitude of medical conditions. Without further clinical information, this simple syndrome taken in isolation is incomplete and unsatisfactory for describing PMR in a way that differentiates it from other diseases.

Since first descriptions there has been an ongoing debate about its pathophysiological status. Is it a benign form of giant cell arteritis (GCA), a precursor of another rheumatic disease, or a distinct disease entity? (2-4) Modern imaging techniques have confirmed that PMR is indeed distinct, showing a characteristic pattern of musculotendinous inflammation. (5) This does not necessarily resolve the question of the nature of its relationship to GCA, since patients with GCA may also show the characteristic imaging features of PMR (6). Both diseases often exhibit systemic features with a marked systemic inflammatory response. Lastly a multitude of non-GCA conditions can mimic PMR - including rheumatoid arthritis, spondyloarthritis, crystal arthritis, myositis and various other non-rheumatic diseases including infection or malignancy.

Arguably, using a trial of glucocorticoids as diagnostic confirmation increases the risk of diagnostic error because so many conditions respond partially or transiently to glucocorticoid therapy. Therefore, it is advisable to make a positive diagnosis of PMR to justify the use of long-term glucocorticoids. (7) In this narrative review, we revisit the history of definitions and descriptions of PMR, its systemic features, and its association with the large vessel vasculitis.

Definitions and descriptions of PMR

In 1957, Barber described twelve individuals aged 46-68 years, including ten women, who had a relatively sudden onset of widespread muscle pains and a high erythrocyte sedimentation rate (ESR). (2) Barber noted that although there were apparent similarities to rheumatoid arthritis, this condition was distinct in that no arthritis or joint destruction occurred despite

several years of observation. Although recognised earlier, this was the first time that this condition had been named '*polymyalgia rheumatica*'.

In 1888, Bruce described five men between the age of 60 to 71 with '*senile rheumatic gout*'. (8) At least three of his cases involved the hands and/or feet and it is doubtful whether they would presently have been diagnosed with PMR. In 1945 Holst and Johansen described shoulder and hip girdle pain and stiffness in five patients between the ages of 40 and 61; they named this '*peri-extra-articular rheumatism*'. (9) In 1952, Meulengracht and Schwartz described 20 people with a shoulder girdle syndrome that they called '*periarthrosis humeroscapularis*'. (10) In 1953, Bagratuni described seven cases of limb girdle pain and stiffness without peripheral arthritis in people between the ages of 57 to 73. (11) He too thought he was observing a unique syndrome which he termed '*a rheumatoid syndrome occurring in the elderly*'. He believed this to be part of the spectrum of rheumatoid arthritis with joint sparing ('*anarthritic rheumatoid disease'*). Therefore, from the earliest descriptions, this disease entity has been framed in two ways. The first framing uses anatomical terms such as "extra-articular / peri-arthritis" to denote that the site of inflammation. The second framing describes similarity or otherwise to more familiar rheumatic diseases such as gout or rheumatoid arthritis. Since 1957, the name for this disease entity has largely stabilised as *polymyalgia rheumatica* - a descriptive term which is agnostic to anatomical localisation but acknowledges its status as a distinct disease entity.

Relationship with age

Descriptions of PMR in literature have long acknowledged its association with aging. The age distribution of PMR closely mirrors that of GCA. This has been taken as indirect evidence of disease association. Barber did describe individuals in their 40s, recalling Horton's original patient with GCA who was just 50 years of age at presentation in 1931. (12) However, early descriptions incorporated the idea that PMR affected older people. William Bruce used the adjective 'senile', and Bagratuni described it as a syndrome occurring in 'the elderly'.

However, "age over 50" is viewed as a near-mandatory criterion for diagnosing both PMR and GCA. It is therefore unknown how commonly PMR occurs in the under-50s. An epidemiological study using administrative codes from a UK primary care research database reported the annual incidence of PMR as being 3.2/100,000 in people in their forties, rising

steeply in those above the age of 80 with an annual incidence of >315/100,000. Cases had to be treated with glucocorticoids to be classified as PMR, so untreated patients would not have been included. (13) Another epidemiological study collating over 30 years of data using a well-curated registry from Olmsted County, Minnesota did not report any cases of PMR under the age of 50 years. (14) This type of epidemiological data therefore largely reflects current ideas about age criteria for PMR and cannot be taken as proof that PMR obeys an age cut-off; only that it is rarely diagnosed in younger age groups.

Relationship with other diseases

From the first descriptions in 1888, it was recognised that this was a condition that lay outside of the known disease categories of 'rheumatoid arthritis' and 'gout and rheumatism'. (8) After the agreement of a name for the disease entity, the next task was to consider which patients should be categorised as PMR. Since the disease was relatively new, there were multiple attempts over subsequent decades to develop classification criteria culminating in an international project that published in 2012.

Bagratuni focused on the relationship of PMR to rheumatoid arthritis, naming it *anarthritic rheumatoid disease.* Two of his fifty patients did develop typical rheumatoid arthritis after 2- and 5-years follow-up. (11) Gordon *et al.* biopsied multiple sites in six patients diagnosed with PMR and confirmed a peri-articular involvement with inflammation of the synovium, joint capsule and peri-arthrous structures, differing from the usual findings seen in rheumatoid arthritis. They noted difficulties in distinguishing PMR from rheumatoid arthritis without long-term follow-up. (15)

In 1965, Andrews reported on ten individuals with PMR who had biopsies of the acromio-clavicular joint, muscle and (in two cases) temporal arteries. No evidence of rheumatoid arthritis or vasculitis was found in any of the biopsies, but he did find a single case of a bronchogenic carcinoma in a 60 year old man underlining the need to consider cancer in these patients. (16)

From the early days the greatest controversy was the nature of the relationship of PMR to GCA. The two diseases had similarities not only in demographics but also regarding the pattern of laboratory markers. High acute phase response including ESR is commonly seen in both diseases. In 1962, Ralph Ross Russell described an 80-year-old man who had biopsy-

proven GCA that had responded to glucocorticoid treatment. Eleven months after diagnosis, he developed a polymyalgic syndrome with an ESR of 103 mm/hour. A biopsy of the deltoid muscle showed histological giant cell arteritis. (17) If a PMR relapse after a diagnosis of GCA could be vasculitic in nature, this naturally led to the question of whether apparently isolated PMR might harbour a similar relationship. To test this proposition, arterial biopsies of patients with PMR were needed. Although Gordon (15) and Andrews (16) had examined biopsies in their studies for vascuiltis, this had not been done systematically and not always including the superficial temporal artery. In the early days, it was difficult to directly test this idea, but some circumstantial evidence appeared to support it.

In 1966, Dixon *et al.* reported biopsies of the superficial temporal arteries in 29 individuals with PMR. Histological features of GCA were seen in 10/29. (18) In 1967, Bruk reported on 80 patients with PMR, whose symptoms began at ages of 42 to 83. He performed arterial biopsies (mostly temporal) in 33 of these, and sternoclavicular joint biopsies in 5, alongside various clinical and laboratory variables. 15/33 arterial biopsies were compatible with GCA. Bruk noted that arterial bruits were present in 12/21 patients with 'definite vasculitis' but only in 3/42 of those not considered to have any vasculitis. (19) However, this was a mixed cohort: 29/80 PMR cases had localised headache, 14 had visual symptoms and five had limb claudication compatible with GCA. Overlap with other rheumatic diseases was suggested by sacro-iliac joint erosions or sclerosis in 8 patients.

Meanwhile in Scandinavia, autopsy studies suggested that subclinical GCA might be common, both in PMR and in the general population. Bengt Hamrin and colleagues found consistent evidence of GCA in biopsies of superficial temporal arteries (3), and also in the aorta and great vessels on autopsy; they coined the term '*polymyalgia arteritica*' to underline that a large number of these individuals had vasculitis. (20) In 1971, a report from a large necroscopy series in Scandinavia by Ostberg revealed vascular appearances of GCA in individuals who had never had a diagnosis of GCA, but records suggested they had PMR-like symptoms during their lifetime. (21)

More recently, a report of 346 individuals with clinical PMR showed ultrasound evidence of GCA in 79 (23%) individuals. (22) A PET-CT study reported that 31 of 337 (9%) patients with clinical PMR had subclinical GCA; although those with vascular FDG uptake were treated with higher glucocorticoid doses, there was no difference in relapses or duration of glucocorticoid treatment. (23)

Does 'PMR with subclinical GCA' represent a phenomenon of GCA perfectly mimicking the clinical presentation of PMR, or can the two inflammatory diseases coexist in their respective vascular and musculoskeletal sites? In 2006, Blockmans et al reported on 18-flurodeoxyglucose (FDG-)PET imaging of patients with GCA, some of whom also had shoulder-girdle symptoms. They found that alongside the vascular uptake, the individuals with shoulder girdle symptoms also had 18-FDG uptake around the shoulder joints, suggesting that peri-arthritis (PMR) and vasculitis (GCA) could coexist. (24) Whether PMR and GCA ought to be considered two facets of the same disease remains uncertain. This may be a normative question of disease classification rather than being an empirically testable hypothesis.

The age restriction of PMR diagnosis means that it is not usually considered whether a syndrome like PMR might similarly coexist with Takayasu arteritis. The relationship between PMR, GCA, and Takayasu's arteritis is a complicated one that can be traced back to the 1960s. Alestig and Barr conducted a biopsy study of ten individuals with muscle aches suggestive of PMR. This cohort included one person with TAK who had a positive temporal artery biopsy (25). TAK is a much rarer disease than both PMR and GCA, and this relationship has not been formally tested, but there is anecdotal evidence that TAK may also present as PMR. (26, 27) A retrospective study found that proximal arthralgia and myalgia as seen in PMR was present in 13% of patients with TAK and 30% of patients with GCA. (28) Patients with TAK will be younger and as discussed above, physicians are unlikely to diagnose PMR in people younger than 50 years of age. It is likely that TAK and GCA may be part of their own spectrum as suggested by their grouping together under the "large-vessel vasculitis". (28, 29) The main discriminant between the two conditions is age. A discussion on this topic is outside the remit of this paper. The Chapel Hill Consensus Conference did not consider PMR as a vasculitis and did not include it within its classification system. (30)

Clinical features and pathology

The onset of PMR is frequently subacute, with symptoms developing over days to weeks. Evidence of systemic inflammation - fever, sweats, weight loss etc. are a common presenting feature of PMR, and elevation of laboratory markers of inflammation is almost universal. However, these systemic features poorly discriminate PMR from GCA or from other serious PMR mimics such as malignancy or infection.

To make a positive diagnosis of PMR, it is necessary to search for localising features of (periarticular) inflammation. Symptoms of PMR are usually described in the literature as pain and stiffness affecting the neck, shoulder and pelvic girdle; bilateral shoulder pain is still often considered a *sine qua non* for the diagnosis. Barber used the German word *Hexenschuss* ("kicked by a witch"), to describe the axial pain. (2) Prolonged stiffness that improves over the day is an important feature of PMR. The clinical term "early morning stiffness" is used for rheumatoid arthritis. The stiffness of PMR has its own unique distribution and nature, presumably reflecting the tendon/ligament-centric inflammation of PMR, rather than the synovio-centric inflammation seen in rheumatoid arthritis. (31) An early report suggested that patients with PMR who report severe stiffness are less likely to have co-existing GCA, but this observation has not been replicated. (18)

Symmetry of symptoms is important; shoulder pain that remains unilateral is less likely to result in a PMR diagnosis. However, the evolution to bilaterality can occur over a few days to weeks. The anatomical site of inflammation may be visualised using 18-FDG-PET scans. Blockmans et al demonstrated 18-fluorodeoxyglucose (18-FDG) uptake in and around the shoulders, hips, and vertebral spinous processes in patients with new PMR. (24) Wakura *et al.* compared this pattern of uptake with that seen in patients who had elderly onset rheumatoid arthritis. The difference in the uptake patterns appears to be related to "entheseal" uptake in PMR versus synovial uptake in rheumatoid arthritis. (32) MRI studies confirm that this is distinct from the enthesitis of the spondyloarthritides, in that osteitis is absent in PMR; the inflammation is focused on the musculotendinous junction. (33) Although synovial biopsy studies in PMR have shown a non-specific inflammatory infiltrate (34), the imaging data and lack of joint destruction suggests that any synovitis is secondary to the primary, extracapsular site of inflammation.

Localising symptoms of PMR are not always localised to the limb girdles. A well-conducted case series of 177 patients describes pain and swelling in knee, wrist, metacarpophalangeal joints and ankles; carpal tunnel syndrome; and the syndrome of remitting seronegative symmetrical synovitis with pitting oedema ("RS3PE"). (35) However, clinical findings of peripheral joint synovitis should always prompt consideration of rheumatoid arthritis.

In studies from the 1990s, the principal cytokine elevated in peripheral blood of untreated PMR was identified as interleukin-(IL-)6. (36) Although it is not the only cytokine involved in PMR, the concentration of IL-6 is higher than that of other cytokines and therefore easier to

detect. IL-6 levels correlate with the burden of inflammation visualised on whole-body MRI of patients with PMR. (37) IL-6 is the main driver of the hepatic acute-phase response, explaining why acute-phase markers including C-reactive protein, fibrinogen, plasma viscosity and ESR tend to be markedly elevated in untreated PMR. IL-6 is an endogenous pyrogen and therefore may play a role in the fever sometimes observed in PMR. (38) IL-6 is also implicated in cancer cachexia via multiple mechanisms, perhaps explaining why cancer is a well-known PMR mimic. (39) IL-6 is also elevated in GCA which may explain why the systemic features of these diseases can be so similar.

Although the pattern of affected tissues in PMR is now well-described by imaging studies, the disease mechanism remains unclear. PMR has been conceptualised both as an autoimmune and an autoinflammatory disease. (36) At the time of writing, the HLA association of PMR has been inconsistent in the small studies that have been published to date. (40, 41) Genome-wide association studies of PMR are awaited and may shed further light on the aetiopathogenesis.

Classifying PMR

The traditional reliance of diagnosis on clinical history and examination, combined with non-specific laboratory tests, means that clinicians, patients and regulators need assurance of the translation of available research to their own context. Classification criteria are one approach to this; the use of consensus-based classification criteria in rheumatology has greatly accelerated research progress because they facilitate regulatory approval of new therapies.

Independent validation of classification criteria in other settings is important and the classification criteria that have undergone validation are shown in Table 1. Other unvalidated criteria which were used as case definitions in cohort studies were defined by Jones & Hazleman (42), and Chuang et al (43). Bird *et al* (44) and Nobunaga *et al* (45) both stated that their criteria were 'diagnostic criteria' but they were not validated in "single-gate" series of patients with suspected PMR, and should therefore still be considered as (historic) classification criteria.

Tellingly, Bird *et al.* (44) considered the overlap between features of PMR and GCA to be a conceptual problem in creating their data-driven criteria for PMR: "many regard the two conditions as part of the same disease spectrum". Ultimately, they compromised by requiring

either three of a list of seven features to be present, or less than three of the seven features but with the additional finding of "temporal artery abnormality". This marginally improved the sensitivity in the validation cohorts but did not change the specificity since GCA was not included in the list of "PMR mimics" that were used as comparators in the criteria development.

The items included in the classification criteria sets form an interesting historical record in the way that PMR was regarded over the years. Common features of these sets included age, bilateral shoulder pain, morning stiffness and an acute phase response (Table 1).

The development of PMR classification criteria culminated in the 2012 provisional ACR/EULAR classification criteria. (46) The candidate items for the criteria were derived via expert clinical consensus and the items finally chosen for the criteria were selected via a data-driven process involving prospective recruitment and follow-up of cases and controls. In a testimony to the robustness of the process, these criteria have successfully been tested in other settings as well. (47-50) In their dataset, the use of ultrasonography did not appear to substantially improve the performance of the criteria, and this was included as an optional item in the final criteria set. This reflects the status of musculoskeletal ultrasound which is still not ubiquitous in routine diagnosis of PMR.

Diagnosing PMR

Clinical diagnosis of PMR can be challenging. There are further challenges when attempting to codify the process of diagnosis in a clinical guideline, in which assumptions must be made about the nuances of meaning and applicability of the terms used and the potential for misinterpretation by readers with a different scope of practice. A survey of UK general practice (51) suggested that the available clinical guidelines provided insufficient guidance for PMR diagnosis, particularly for atypical presentations of PMR. Due to the unselected nature of general practice, an individual GP will see a new case of PMR only infrequently, and therefore has less opportunity to acquire and reinforce the tacit knowledge about PMR that comes with clinical experience of a condition.

Clinical diagnosis in rheumatic conditions is a complex process utilising both explicit and tacit knowledge which is applied in a deeply contextual way. (52) Rheumatic conditions are often complex and multi-system. A best match diagnosis may be preferable to leaving a patient

undiagnosed and untreated. Diagnostic criteria therefore ought to be broad, inclusive and yet non-overlapping (usually implemented via a “no better explanation” clause). On the other hand, classification criteria are primarily designed to create well-defined, homogenous groups for the purpose of making clinical research translatable to a particular demographic. The high specificity of the classification criteria comes at the cost of sensitivity, unless the diagnosis is made by a simple cutoff along a scale. (52) Classification criteria are often used for clinical teaching, to concisely communicate the key features of a disease, but it is crucial to stress that they should not be used as simple checklists for making diagnoses in clinical practice (52). In the context of PMR, in the early years physicians had to rely principally on the result of a single blood test (ESR) interpreted in the light of finely-honed clinical skills. The skills of elicitation of clinical signs that may suggest alternative pathologies – for example, rotator cuff tendinopathy, shoulder osteoarthritis, peripheral synovitis, arterial murmurs, inflamed cranial arteries, or carotidynia - are still a fundamental part of diagnosis of PMR, as well as identifying its comorbidities and its various mimics.

The major change from the original descriptions of PMR is the use of imaging to complement clinical skills. Ultrasonography, magnetic resonance imaging and 18FDG-PET have all been suggested as ways of reducing diagnostic uncertainty in PMR. (53, 54) However, this leaves the question of how to manage a patient presenting with clinical and laboratory features of PMR, if the imaging tests employed do not support either a diagnosis of PMR nor an alternative explanation for symptoms. In a study of 22 patients who were diagnosed with PMR by expert rheumatologists, fulfilled validated classification criteria, responded to glucocorticoid treatment and no better explanation for symptoms emerged over a year of follow-up, only 14/22 showed the characteristic extracapsular pattern of PMR on MRI. This subgroup was more likely to report a complete response to glucocorticoid therapy and was also more likely to relapse during the first year of glucocorticoid taper. (37) That study was limited by absence of vascular imaging, so it is not known whether some may also have had co-existing large-vessel vasculitis. Hypothetically, if some of these patients’ presenting symptoms were caused by vasculitis rather than musculoskeletal inflammation, but if they responded to “PMR dose” glucocorticoids taper, should they have been labelled as PMR, GCA or another, new diagnostic category?

It is difficult to provide universal imaging guidelines, since accessibility and expertise for each modality differs widely between secondary care centres. If imaging is to be used, timely access

is particularly crucial since glucocorticoid therapy can reduce or abrogate the signs of inflammation that most of these imaging modalities are able to detect. “Fast track pathways” to secondary care are an attractive solution but are subject to postcode lottery. (55) Creation of entirely new pathways within resource-constrained, centrally funded healthcare systems is not straightforward. Multi-stakeholder engagement at local, regional and national levels is advisable in order that all possible options for change may be explored. Adaptation of existing pathways may be preferred but carries risks that trade-offs and assumptions “baked in” to the pathway may not be appropriate to translate to patients with suspected PMR.

Conclusion

PMR was probably first described (although not so named) by Bruce in 1888. During these 136 years, there has been an evolution in its nosology and the way PMR is conceptualised. The identification of a characteristic imaging pattern of PMR – involving tendons, ligaments and the joint capsule, with probable inflammatory spillover into adjacent synovial-lined structures – has confirmed the status of PMR as a disease entity and highlighted the need to improve diagnostic specificity in clinical practice and to improve support for primary care colleagues who may see PMR infrequently. (13, 51)

Another common thread running through the historical literature is that features of PMR and GCA may coexist in some patients: older biopsy studies and modern imaging studies suggest that simultaneous inflammation of the musculotendinous structures (“PMR”) and the larger blood vessels (“GCA”) may be present in a subset of patients with a clinical diagnosis of isolated PMR - or indeed, isolated GCA. If glucocorticoid monotherapy were the only treatment option, perhaps this would not matter. But the advent of licensed targeted therapies for PMR in the USA (56) has led to renewed attention to improve the accuracy of PMR diagnosis. The value of early referral to a rheumatologist has been endorsed by an international group of experts (55). There have been calls to update existing PMR guidelines and recommendations (57-59). The recognition that some patients presenting clinically with PMR may have imaging features of GCA, without classical symptoms or signs of GCA, poses new challenges for clinical pathways. It is important to ensure that this does not produce misuse of GCA protocols (e.g. immediately prescribing high-dose glucocorticoids), without taking time to verify diagnosis. In this rapidly-evolving landscape, it will be essential to work

with all stakeholders, including patient groups, to ensure we can better meet the needs of all patients with PMR. (7)

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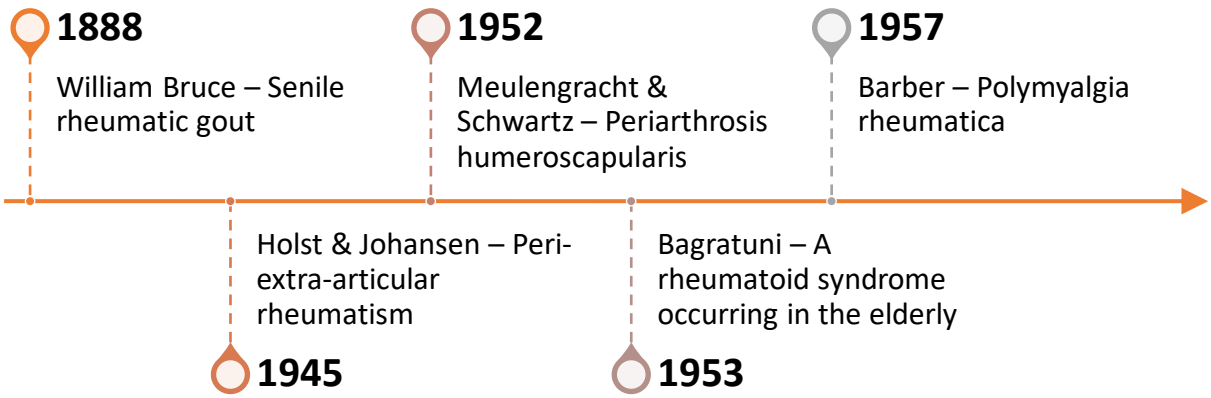

Figure 1: Other names for polymyalgia rheumatica prior to 1957.

Table 1 Classification criteria for PMR

	Bird et al (44)	Nobunaga et al (45)	Dasgupta et al (46)	
Year	1979	1989	2012	
Demographic				
Age	✓ (>65)		✓ (>50)[%]	✓ (>50)[%]
Clinical features				
Duration <2 weeks	✓			
Duration ≥2 weeks		✓[^]		
Neck pain		✓[&]		
Bilateral shoulder pain or stiffness	✓	✓[&]	✓[%]	✓[%]
Bilateral upper arm tenderness	✓			
Bilateral upper arm pain		✓[&]		
Bilateral hip pain		✓[&]		✓ (or reduced ROM)
Bilateral thigh pain		✓[&]		
Morning stiffness	✓ (>1 hour)		✓ (>45 minutes)[$]	✓ (>45 minutes)[$]
Hand synovitis absent		✓		
Other joint involvement absent (besides shoulders and hips)			✓	✓
Depression	✓[*]			
Weight loss	✓[*]			
Laboratory markers				
Abnormal ESR	✓ (>40mm/1st hour)	✓ (>40mm/1st hour)	✓[*%]	✓[*%]
Abnormal CRP			✓[*%]	✓[*%]
Normal muscle enzymes		✓		
Negative RF and ACPA			✓[$]	✓[$]

Ultrasonography				
1 hip + 1 shoulder abnormality				✓*
Bilateral shoulder abnormality				✓*
Standard for positive case definition	3/7	4/4	4/6	5/8

* Presence of either/both would count as 1 point; & presence of any two would be count as 1 point; ^ is a defining characteristic of the anatomical distribution and not a separate criterion by itself; % mandatory criterion; $ double points; ROM = range of movement; RF = rheumatoid factor; ACPA = Anti Cyclic citrullinated peptide antibody; Ultrasonography abnormalities include subdeltoid bursitis, bicipital tenosynovitis, glenohumeral synovitis, hip synovitis, and trochanteric bursitis.