The real evidence for polymyalgia rheumatica as a paraneoplastic syndrome

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SUMMARY

The aim of this study was to systematically consider the evidence for polymyalgia rheumatica (PMR) as a paraneoplastic disease.

A systematic review of Medline and Embase was conducted from their inception to February 2017. Risk of bias was assessed using the Newcastle-Ottawa tool. Data were extracted regarding the PMR-cancer association, the types of cancer associated with PMR and the presentation of PMR patients subsequently diagnosed with cancer. Twenty-three full text articles were reviewed from the 1174 unique references identified in the search. Nine articles were included in the final review. There was some evidence of an association between PMR and cancer in the short-term (first 6 to 12 months after diagnosis), but no evidence of an association after this time. Limited evidence suggests that lymphoma, prostate and haematological cancers may be those cancers more commonly diagnosed in those with PMR. There was little evidence to suggest what presenting features may be associated with the development of cancer.

There is little evidence of PMR as a true paraneoplastic disease. However, there is reason to be cautious when making the diagnosis of PMR. Clinicians should be aware of this potential association both prior to making a diagnosis and throughout the course of the condition.

Key words: *Polymyalgia rheumatica; Paraneoplastic syndrome; Cancer; Systematic review.*

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INTRODUCTION

Polymyalgia rheumatica (PMR) is a relatively common inflammatory rheumatological disorder of older (>50 years) adults. Classical presenting symptoms include bilateral hip and shoulder girdle pain and stiffness, morning stiffness, raised inflammatory markers [classically elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)] and systemic features such as pyrexia, fatigue and weight loss (1). In the absence of a gold standard diagnostic test, PMR remains a clinical diagnosis. Current guidelines from the British Society for Rheumatology, and others, suggest that a variety of disorders should be excluded prior to making a diagnosis of PMR (2-4). These include other rheumatological conditions (including rheumatoid arthritis and fibromyalgia), endocrine diseases (*e.g.*, hypothyroidism) and neurological conditions (*e.g.*, Parkinson's disease), drug-induced myalgia (*e.g.*, from statin treatment), infection and *active cancer*. Definitively excluding *active cancer* can be challenging and although simple screening investigations, such as a chest X-ray, are advocated by guidelines, more complex and invasive investigations are not indicated for all patients.

The association between cancer and rheumatic disorders has long been recognised. Racanelli et al. (5) summarise these into three groups. First, patients where a rheumatic disorder is directly triggered by a tumour or its metastases (*e.g.* leukaemic synovitis); second, patients with an established rheumatic condition who are at increased risk of a specific malignancy [*e.g.*, primary Sjögrens syndrome and lymphoma (6)]; and third, patients with paraneoplastic diseases. This group arises where an apparently idiopathic rheumatic disease is actually the expression of an occult cancer that becomes clinically evident within a defined timeframe [usually 2 years (7)]. Thus

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a paraneoplastic syndrome is the term used to describe the clinical or systemic symptoms that are associated with a tumour but not caused by direct invasion of the target tissue.

Paraneoplastic syndromes are thought to be caused by an altered immune response, either caused by antibody production (*e.g.*, anti-Hu antibody syndrome and lung cancer, which presents as neuropathies) (8), aberrant hormone release [*e.g.*, syndrome of inappropriate anti-diuretic hormone secretion, SIADH and lung cancer, leading to headache, weakness and low sodium levels (9)] or abnormal cytokine release such as vascular endothelial growth factor (VEGF) (7).

Studies suggest that up to 8% of patients with cancer may have a paraneoplastic syndrome (9). Symptoms of a paraneoplastic syndrome can affect any organ system, including haematological (*e.g.*, haemolytic anaemia), cutaneous (*e.g.*, scleroderma, clubbing), vascular (*e.g.*, leucocytoclastic vasculitis, Raynaud's phenomenon) and neurological systems (*e.g.*, neuropathies or encephalomyelitis, stiff-man syndrome) (10). Common rheumatological manifestations include hypertrophic osteoarthropathy, cancer associated myositis, paraneoplastic polyarthritis, and relapsing seronegative symmetric synovitis with pitting oedema (RS3PE) (6).

However, for less specific symptoms, such as joint pain, establishing whether these are truly paraneoplastic is more controversial. Lortholary et al. (11) define a paraneoplastic syndrome using the following criteria:

1. presence of a cancer;
2. clinical presentation not directly due to the primary tumour or metastases;
3. absence of other non-neoplastic causes;
4. parallel evolution.

A paraneoplastic syndrome is considered probable if three criteria were met and possible if one or two criteria were met.

For a condition such as PMR, which has no specific diagnostic test, establishing whether there is a true association between PMR and malignancy or whether it is a co-incidental existence of the two conditions is more difficult. Classically symptoms of a paraneoplastic syndrome regress after treatment of the underlying cancer. However, given the often rapid improvement of PMR symptoms with low dose glucocorticoids, proving such temporality is unethical and inappropriate.

Given the controversy about whether this represents association or co-incidence, this review will consider the evidence for the association between PMR and cancer. Specifically, it will consider timescales and whether any presenting features were associated with a later diagnosis of cancer to further elucidate the evidence surrounding the paraneoplastic syndrome and PMR (12).

MATERIALS AND METHODS

Search strategy

Our search strategy was based on that developed by Ungprasert et al. (13). The search was conducted in Medline (1946 February 2017) and Embase (1974 February 2017). Full details can be found in the Appendix, but briefly the exploded MeSH term *polymyalgia rheumatica* was used in combination with text word searches for polymyalgia and PMR. This was combined with searches for the exploded MeSH term *neoplasms* and text word searches for neoplasm, cancer, malignancy, carcinoma, tumour and other appropriate terms.

Inclusion and exclusion criteria

Inclusion criteria were:

1. cohort study (prospective or retrospective) or randomised controlled trial including an exposed (PMR group) and an unexposed (non-PMR group), or a systematic review;
2. consider the association between a diagnosis of PMR and concomitant or subsequent diagnosis of cancer.

Exclusion criteria were:

1. case reports, case series or case-control study;
2. association between PMR and cancer/paraneoplastic syndrome not considered;
3. no full text article available (*e.g.*, conference abstract), or no English language version of full paper available.

Study selection

Retrieved titles were screened against the inclusion and exclusion criteria by a single

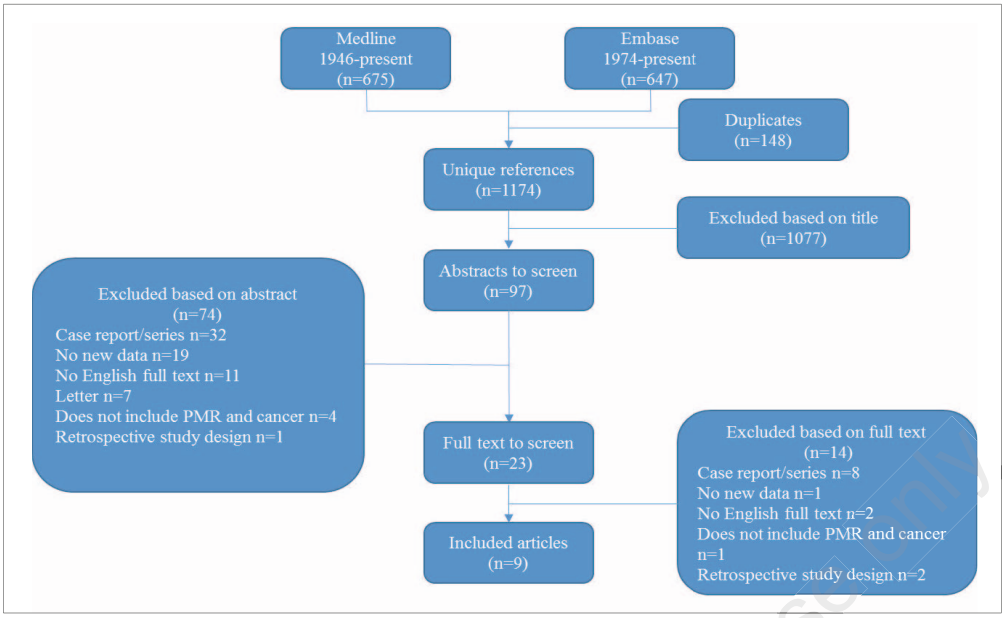

Figure 1 - Selection of articles for systematic review.

reviewer (SM). The abstracts of the remaining studies were then examined with studies not meeting the inclusion criteria excluded. Reasons for exclusion were recorded. Finally, full texts of the remaining studies were reviewed and a final list of included studies was prepared (Figure 1).

Quality assessment

Assessment of study quality and the likelihood of bias was conducted using the Newcastle-Ottawa scale (14). This scale uses a star rating so that each study receives a maximum score of four stars for sample selection (whether the sample is representative of the population of interest and how exposure is ascertained), two stars for comparability and three stars for outcome (how outcome was assessed and over what time period). For the purposes of this review, we discounted the comparability section, as it relates to control of potentially confounding factors, which we did not consider relevant to our question regarding an association between PMR and cancer, as we did not require this association to be causal.

Data extraction

Data regarding the following were extracted from each study included in the review:

1. time frame between diagnosis of PMR and diagnosis of cancer;
2. types of cancer associated with PMR;
3. presentation of PMR that was later considered to be cancer, focussing particularly on clinical presenting features (*e.g.*, failure to respond to glucocorticoid treatment);
4. the authors' conclusions as to the nature of any PMR-cancer association.

RESULTS

Results of the search

A total of 1174 unique citations were obtained (Figure 1). 1077 were excluded based on title screening and further 74 were excluded after abstract screening, leaving 23 full articles for review. After this final stage of screening, nine studies remained. The main reasons for exclusion of studies at the abstract and full text screening stages were that articles presented case reports or case series (n=40), that no original data or a systematic review were presented (n=20) or that a full paper was not available in English (n=13).

Articles included in the review

Eight of the nine articles identified through the systematic search described cohort stud-

ies (Table I) (15-22). Two articles utilised the same dataset, but with one considering the outcomes of cancer diagnosis and the other causes of death including cancer (19, 20). Five of the articles (17-20, 22), all from Scandinavia, used an unexposed group taken from a database separate to the PMR group, but representative of the general population, whilst two studies [one from the UK (15), one from the USA (21)] selected an unexposed group from the same clinical source data as the exposed PMR group (Table I). A final study from Italy selected controls from the same hospital, but with a diagnosis of

Table I - Description of studies included in the systematic review.

	Muller et al. (15)	**Bellan et al. (16)**	**Haga et al. (17)**	**Ji et al. (18)**
Study location	**UK**	**Italy**	**Norway**	**Sweden**
Year	**2014**	**2017**	**1992**	**2010**
Definition of PMR	Aged ≥50 years. Read code for PMR in GPRD 1987-1999. ≥2 oral corticosteroid prescriptions within 6 months of Read code. No pre-existing vascular disease or cancer at PMR diagnosis	Diagnosed with PMR in tertiary clinic. ≥2 years follow-up data	Diagnosed in hospital 1978-1983. PMR not differentiated from TA Pain/stiffness in proximal muscles for ≥4 weeks; ESR≥40mm/h; No evidence of muscle disease, CTD or infection	Hospitalised with PMR/ GCA 1969-2006 (SHDR). PMR not distinguished from GCA
Sample size of PMR group	2877	100	185: 91 PMR only, 54 TA only, 40 PMR+TA	35,918
Mean (SD) age of PMR sample (years)	72.0 (8.9)	73.2 (7.8)	69.6 (range 43-86)	-
% of PMR sample female	72.7	60	70.8	-
Follow-up time in PMR group (years)	Median 8.4 (IQR 3.9, 12.3)	-	-	Median 8 (range 0-35)
Definition of comparator group	Matched (year of birth, gender, general practice) from GPRD. No pre-existing vascular disease or cancer at matched PMR patient's diagnosis	Diagnosed with osteoarthritis in tertiary clinic ≥2 years follow-up data	Matched (year of birth, sex) from Central Population Registry to PMR group. Alive at time of PMR diagnosis and living in same county	No defined group
Sample size of comparator group	9422 (4:1 matched)	702	5:1 matched to PMR group	N/A
Mean (SD) age of comparator sample	71.5 (9.1)	61.3 (12.8)	-	N/A
% of comparator sample female	72.8	82.5	-	N/A
Follow-up time in comparator group	Median 7.6 (IQR 3.3, 12.3)	-	-	N/A
Ascertainment of cancer outcome	Read code for "neoplasm" (chapter B, excluding B7 codes (non-malignant neoplasms) in GPRD	Record review	Cancer Registry of Norway until end 1987, regardless of date of PMR/TA diagnosis. Some cancers are before PMR/TA diagnosis	Swedish Cancer Registry up to 2006. Expected number of cancers calculated based on national population size
Quality assessment (Newcastle-Ottawa scale)				
Selection	4	2	4	2
Outcome	3	3	2	3

TA, temporal arteritis; GCA, giant cell arteritis; SHDR, Swedish Hospital Discharge Register;
GPRD, General Practice Research Database; ESR, erythrocyte sedimentation rate; CTD, connective tissue disease;

osteoarthritis (16). All studies used a clinical diagnosis of PMR, ascertained from the medical records, whilst six of the studies also used specified criteria for inclusion (15, 17, 19-22). Four of the articles explicitly stated that they did not differentiate PMR from giant cell arteritis (GCA) (17-20), one study included only those patients with PMR symptoms and a negative temporal artery biopsy (22). In the remaining three studies, it was not clear whether those with concomitant GCA were excluded, but all patients were required to have PMR (15, 16, 21). All cancer diagnoses were obtained by medical record review

Myklebust et al. (19)	**Myklebust et al. (20)**	**Pfeiffer et al. (21)**	**Schauffelberger et al. (22)**
Norway	**Norway**	**USA**	**Sweden**
2002	**2003**	**2015**	**1995**
Diagnosed by rheumatologist/ in hospital with PMR or TA or hospitalised with another condition 1987-1997. Fulfilled Bird or Hamrin criteria. Included those with cancer diagnosed around time of PMR diagnosis if PMR criteria fulfilled	Diagnosed by rheumatologist/in hospital with PMR or TA or hospitalised with another condition 1987-1997. Fulfilled Bird or Hamrin criteria	Rochester Epidemiology Project. PMR diagnosed by physician 1970-1999. ≥50 years; bilateral aching and morning stiffness ≥30 minutes in ≥2 of: neck/ torso, shoulders/proximal arms, hips/ proximal thighs; ESR>40mm/h. Definite response to <20mg/d corticosteroids. Excluded if alternative diagnoses	Hospital patients 1985-1987 screened negative for temporal artery abnormalities. Pain and stiffness in ≥2 groups of proximal muscles for ≥2 weeks. No inflammatory arthritis. ESR≥40mm/h. ≥50 years. No evidence of infection, malignancy, RA, SLE, periarteritis nodosa
398 (315 PMR only)	315	359	220
-	Female 72.4 (8.2); Male 71.2 (8.5)	73.5 (8.5)	72.9 (range 50-91)
68.6 overall, (67.6 PMR only)	67.6	66.6	71
-	Total follow-up time 1747 years	Mean 11.8 (SD 6.7)	Mean 36 months (range 0-52, median 36.8 months)
Matched (month and year of birth) from Central Population Registry. Alive at time PMR diagnosis	Matched (month and year of birth) from Central Population Registry. Alive at time PMR diagnosis	Matched (year of birth, sex, length medical history) from Rochester Epidemiology Project	*Matched normal population of the same age*
1592 (4:1 matched)	1260 (4:1 matched)	357	Unclear
-	-	73.3 (8.5)	-
68.6	-	66.9	-
NS	Tempo di follow-up totale di 6656 anni	Media 10,7 (SD 7,4)	Unclear
Cancer Registry of Norway until end 1998. All cases of cancer included. Type, time and site of cancer recorded	Date and cause of death from Statistics Norway. Cancer could be among causes of death	Record review cross-referenced with Mayo Clinic Cancer Registry. Date, type and site of malignancy recorded	Derived from medical and death records. Only fatal cancers considered
4	4	3	3
3	3	3	3

RA, rheumatoid arthritis; SLE, systematic lupus erythematosus;
IQR, inter-quartile range; SD, standard deviation; N/A, not applicable.

(either clinical records or cancer registration databases). All studies except Ji et al. (18) gained three or four stars for cohort selection when assessed using the Newcastle-Ottawa criteria and all except Haga et al. (17) gained the full three stars for outcome ascertainment.

What is the evidence of an association between PMR and cancer?

The methods of comparing and reporting the association between PMR and cancer varied greatly, as did the findings. Five of the studies found there to be no difference in the rates of cancer diagnoses in those with and without PMR (17, 19-22). Two reported an increase in cancer diagnoses in PMR patients compared to those without PMR. Bellan et al. (16) reported an odds ratio of 5.1 (95% CI 2.9, 8.9) for their tertiary care PMR group to be diagnosed with cancer compared to the comparator group and Ji et al. (18) showed a standardised incidence ratio of 1.19 (1.15, 1.23) in their hospital population with PMR compared to the general population (Table II). Muller et al. (15) reported that whilst the risk of a cancer diagnosis decreased over time, there was a significant increase in the risk of cancer in the first six months after a PMR diagnosis [hazard ratio 1.69 (1.18, 2.42)], but the risk was then attenuated [1.03 (0.70, 1.51) at 6 to 12 months after PMR diagnosis]. A higher risk closer to the time of initial PMR diagnosis was also noted by Ji et al. (18).

The final study identified was a systematic review and meta-analysis of malignancy in

Table II - Association of PMR with cancer.

	Muller et al. (15)	Bellan et al. (16)	Haga et al. (17)	Ji et al. (18)	Myklebust et al. (19)	Myklebust et al. (20)	Pfeiffer et al. (21)	Schauffelberger et al. (22)
Incidence of cancer outcome in PMR group	23.2% (no timescale given)	24% (no timescale given)	Unclear	3941 cases	8.6% (males 13.4%, females 7.5%)	3.2% (no timescale given)	10 year cumulative incidence (SD) Any: 13.8 (2.0) Solid: 13.1 (1.9) Haematologic: 1.2 (0.6)	Observed number of cancer deaths 6
Incidence of cancer outcome in comparator group	19.5% (no timescale given)	5.8% (no timescale given)	Unclear	N/A	11.1% (males 14.5%, females 10.8%)	5.2% (no timescale given)	10 year cumulative incidence (SD) Any: 13.1 (2.0) Solid: 11.4 (1.8) Haematologic: 1.1 (0.6)	Expected number of cancer deaths 5
Relative rate of cancer/ paraneoplastic outcomes in PMR versus comparator group	0-6 months: 1.69 (1.18, 2.42) 6-12 months: 1.03 (0.70, 1.51) 1-2 years: 1.04 (0.77, 1.40) 2-5 years: 1.04 (0.86, 1.26) 5-10 years: 1.11 (0.95, 1.30) 10+ years: 1.00 (0.82, 1.23)	OR 5.1 (95% CI 2.9, 8.9)	"Risk of developing cancer not significantly different for the patients with PMR and TA compared to controls"	Overall SIR 1.19 (1.15, 1.23) In first year 2.26 (2.10, 2.42) After first year 1.03 (1.03, 1.10)	RR 0.86 (0.59, 1.26)	RR of death from cancer 0.59 (0.3, 1.17)	p=0.89	Described as non-significant

patients with PMR and GCA (13). These authors included four (15, 17-19) of the eight studies described above. The studies of Bellan et al. (16) and Pfeiffer et al. (21) were published in the interim period, whilst the studies of Schauffelberger et al. (22) and Myklebust et al. (20) were not included, (possibly because of a poorly defined unexposed group and outcome was being death from cancer, rather than a cancer diagnosis respectively).

Ungprasert et al. (13) found a pooled increased cancer risk of 14% (risk ratio 1.14; 95% CI 1.05, 1.22). In the first 6 to 12 months after PMR/GCA diagnosis, they calculated this increase in risk to be 116% (2.16; 1.85, 2.53). However, after removing the study that included only those hospitalised with PMR/GCA (18), these risk ratios were reduced. This resulted in a significantly increased risk in only the first 6 months to a year after initial PMR diagnosis [overall 1.08 (0.99, 1.17); 0 to 6-12 months post-diagnosis 1.76 (1.25, 2.46)].

Which cancers show an association with PMR?

Even the largest studies identified did not have sufficient power to confidently evaluate which cancers were most common in

Table III - Types and sites of cancer associated with PMR.

Muller et al. (15) **Rate per person year (95% CI)**	**Ji et al. (18)** **SIR (95% CI)**	**Pfeiffer et al. (21)** **Cumulative incidence at 10 years (SE)**
In first 6 months Lymphoma PMR (n=1): 3.32 (0.47, 24.0) Non-PMR (n=1): 0.09 (0.01, 0.64) All blood PMR (n=3): 0.70 (0.23, 2.18) Non-PMR (n=3): 0.35 (0.11, 1.07) Urinary tract PMR (n=3): 0.36 (0.12, 1.12) Non-PMR (n=4): 0.17 (0.07, 0.46) Female reproductive PMR (n=3): 0.75 (0.24, 2.34) Non-PMR (n=7): 0.31 (0.15, 0.64) Prostate PMR (n=5): 0.26 (0.11, 0.63) Non-PMR (n=4): 0.07 (0.03, 0.19)	*Overall* Non-Hodgkins Lymphoma 1.32 (1.14, 1.52) Leukaemia 2.16 (1.80, 2.58) Acute myeloid leukaemia 2.69 (2.01, 3.52) Melanoma 1.23 (1.02, 1.48) Squamous cell 1.50 (1.33, 1.69) Stomach 1.27 (1.07, 1.50) Kidney 1.56 (1.30, 1.85) Endometrium 0.81 (0.66, 0.98) Nervous system 1.27 (1.02, 1.56) Prostate 1.38 (1.27, 1.49) Endocrine glands 1.51 (1.20, 1.88) Myeloma 1.48 (1.17, 1.86) *In first year* Leukaemia 5.20 (3.53, 7.39) Acute myeloid leukaemia 7.20 (4.02, 11.90) Squamous cell 1.92 (1.36, 2.63) Connective tissue 4.92 (2.34, 9.08) Colon 1.56 (1.16, 2.06) Stomach 2.21 (1.47, 3.20) Liver 2.57 (1.72, 3.69) Pancreas 1.76 (1.04, 2.79) Kidney 5.07 (3.71, 6.77) Bladder 2.39 (1.71, 3.25) Ovary 2.34 (1.42, 3.61) Lung 2.79 (2.16, 3.54) Prostate 3.33 (2.84, 3.87) Endocrine glands 4.05 (2.53, 6.14) Myeloma 4.42 (2.83, 6.58) *After first year* Non-Hodgkins Lymphoma 3.46 (2.58, 4.54) Leukaemia 1.81 (1.45, 2.22) Acute myeloid leukaemia 2.15 (1.52, 2.96) Melanoma 11.25 (1.02, 1.51) Squamous cell 1.92 (1.36, 2.63) Prostate 1.15 (1.05, 1.25)	*Solid* PMR 13.1 (1.9) Non-PMR 11.4 (1.8) *Haematologic* PMR 1.2 (0.6) Non-PMR 1.1 (0.6)

SIR, standardised incidence ratio; CI, confidence interval.

the early stages after a diagnosis of PMR. However, limited evidence suggests that haematological and prostate cancers and lymphoma may be the most commonly diagnosed in those with incident PMR (15, 16, 18) (Table III).

What evidence is there to identify those with potential paraneoplastic PMR?

There was little evidence provided by the included studies as to the presentation of PMR patients subsequently diagnosed with cancer. However, Bellan et al. (16) reported that the odds of cancer were significantly higher in those aged over 75 years (OR 2.56; 95% CI 1.0, 6.58), males (2.80; 1.10, 7.20) and those with more than 6 tender joints (5.85; 1.65, 20.69).

Author's conclusions as to the nature of the PMR-cancer relationship

The authors of the studies varied in their interpretation of the associations they found between PMR and cancer. Haga et al. (17) and Myklebust et al. (19) considered the average length of time from PMR diagnosis to cancer diagnosis to be too long (greater than three years in both studies), to represent a paraneoplastic phenomenon. Bellan et al. (16) reported that in the 17 patients successfully treated for cancer, 8 experienced a resolution in their PMR symptoms, which may indicate a paraneoplastic effect of PMR. Muller et al. (15) did not consider paraneoplastic syndrome, but suggested that cancer may initially be misdiagnosed as PMR, whilst Myklebust et al. (19) raised the possibility of surveillance bias giving rise to a PMR-cancer association. However, they described the association as likely being coincidental.

DISCUSSION

Statement of principal findings

There have been numerous reports in the literature of the co-occurrence of PMR with various malignant diseases. These have highlighted the potential paraneoplastic nature of PMR (23), the chance occurrence of both conditions and the potential for PMR to have a transformative neoplastic effect (24) *via* an altered immune response (as seen in conditions such as primary Sjögren's syndrome or rheumatoid arthritis), dependent on the time scales involved. Furthermore the condition RS3PE (remitting seronegative symmetrical synovitis with pitting oedema), which has clinical features which overlap with both seronegative rheumatoid arthritis and PMR is considered to be a paraneoplastic rheumatic disease caused by over-production of VEGF (7).

Our review found some evidence of a short-term association between PMR and cancer (less than 6 to 12 months after PMR diagnosis). Whilst this raises the possibility of PMR as a paraneoplastic syndrome, definitive evidence is still lacking, given that PMR remains a clinical diagnosis and there is little evidence in the literature that PMR symptoms resolve following cancer treatment. Also, notwithstanding any other diagnoses, the symptoms of PMR may still rapidly improve with low dose glucocorticoids. In patients with RS3PE (which may resemble PMR), the response to glucocorticoids in those with paraneoplastic disease is thought to be poor (25). In the medium to long term, the evidence regarding an association between PMR and cancer is mixed. The observed association between PMR symptoms and malignancy may represent misdiagnosis of a malignancy as PMR, or coexistence of two conditions in the same individual, either coincidentally, or as result of an underlying susceptibility (*e.g.*, dysregulated immune system).

Furthermore there may be some surveillance bias, given that current guidelines suggest that malignancy should be excluded before the diagnosis of PMR can be made (2). This is particularly likely in those studies, where data are taken from routinely collected clinical or registry data, as it is not clear what investigations might or might not have been carried out on the unexposed group. This type of data provides the basis for the vast majority of the studies included in our review. However, the strongest association between PMR and cancer was seen in the study of Bellan et al. (16) where the unexposed group consisted

of people attending a secondary care clinic with a diagnosis of osteoarthritis. Hence, they are likely to also have undergone additional tests, although not necessarily the same ones as those diagnosed with PMR.

In the papers included in this review, we were unable to find any convincing evidence of clinical presentations that might be suggestive of cancer. Bellan et al. (16) provided some data on this issue, but the data were not clearly presented and their conclusions are contradicted by other studies in the wider literature (1, 26). There is considerable disagreement between studies as to what presenting features may suggest that further investigation is warranted.

Strengths and weaknesses of the study and in relation to other studies, discussing particularly any differences in results

Whilst we took a systematic approach to identifying the literature relevant to the question of whether PMR is associated with cancer, our review still has a number of limitations. Primarily, it was difficult to decide how to specify our inclusion and exclusion criteria and to apply them in practice - specifically with regard to what to consider a research study and what to consider a case-series. We overcame this difficulty by adopting the approach of Ungprasert et al. (13), and including only those papers with a comparator group without PMR in our formal review. However, in forming our conclusions, we have considered the wider literature, which included a number of sizable case series and case reports.

Also of note is that of the three studies finding a significant association between PMR and cancer, two were the largest in the review by some way (15, 18). Whilst the additional power provided by a larger study does not necessarily make this finding surprising, the post hoc power calculation provided by Muller et al. (15) suggests that this study has sufficient power to detect a relatively small hazard ratio of 1.2. However, even these large studies were not able to confidently suggest the types or sites of cancer likely to be associated with PMR-like symptoms.

Our systematic review excluded a large number of case reports and a number of case-series and case-control studies. Whilst it is difficult to make sense of the case report literature in a systematic way, there are some cancers that are frequently encountered in relation to PMR in this literature; leukaemias (24, 27-30), myelomas (30-36), lymphomas (30, 37-40) and lung cancer (41-45). Whilst we know that there is likely to be substantial publication bias in relation to case reports, it is not known what impact this might have. For example, it may be that more cases are noted and published when they involved the immune-related cancers known to be associated with other rheumatological conditions, such as rheumatoid arthritis and lymphoma, or it may be that these are less likely to be published in favour of cancers that have not previously been associated with rheumatological disorders. The types of cancer identified from the papers included in our systematic review are broadly similar to those that appear commonly in the literature.

A recent review and case series concluded that PMR is not a paraneoplastic phenomenon and that the important thing was to conduct a rigorous diagnostic work-up before making the PMR diagnosis (1). This conclusion was based on a comparison of their clinical case series to studies in large databases, including those included in this review, specifically those by Ji et al. (18) and Muller et al. (15). Whilst we agree that there is a clear need to fully assess a patient before making a diagnosis of PMR and that this should likely include screening for common cancers, it is worth noting that the comparison of cancer diagnosis rates made in this paper is flawed, as it compares absolute to relative rates, and that the rates of cancer diagnoses are not as high in other cohorts as the authors suggest.

Meaning of the study: possible mechanisms and implications for clinicians or policymakers

This study suggests that there is evidence of a short-term (<12 months) association between PMR and an underlying malignancy,

although there is insufficient evidence to label this as truly paraneoplastic. Given the non-specific nature of common PMR symptoms, such as shoulder and hip girdle pain and stiffness, fatigue and weight loss, which may also occur in patients with malignancy, establishing a definitive paraneoplastic diagnosis may be challenging. Some of these symptoms may be mediated by cytokine release such as IL-6 and VEGF, which may occur in both conditions (6, 7).

These findings support the guideline suggestions regarding excluding cancer, suggesting that relative simple, economic tests such as a chest X-ray in a smoker, or a prostate specific antigen (PSA) may be warranted as part of the diagnostic work up of PMR. However, the relative lack of association of specific cancers suggests that more complex and costly investigations are not indicated for all patients. Clinicians however should be mindful of this PMR-cancer association and consider additional investigations for a potential malignancy. However, we were unable to find convincing evidence as to which patients may be at highest risk of having a malignancy underlying their PMR symptoms.

Unanswered questions and future research

Despite a number of large studies and a systematic review and meta-analysis, there is not the evidence to suggest that PMR fulfils strict criteria as a paraneoplastic syndrome, particularly given the lack of evidence of improvement with treatment of the malignancy. However, although not truly paraneoplastic, there does appear to be a short-term association between PMR-like symptoms and malignancy. It would therefore seem prudent for future work to concentrate on identifying those patients presenting with PMR-like symptoms who are most likely to experience a cancer diagnosis in the short-term and to attempt to elucidate the cancers most likely to be associated with a PMR-like presentation. This would better enable clinicians to target specific cancer screening in a clinical and cost effective manner to those most likely to benefit, during diagnostic work up.

CONCLUSIONS

In reality, except for intellectual curiosity, it is probably immaterial whether PMR represents a true paraneoplastic syndrome, or if it is just that the early symptoms of some cancers are difficult to distinguish from *true* PMR. What matters is that the correct diagnosis is made early, so that appropriate treatment can be initiated. With this in mind, we suggest that when PMR is the suspected, or even obvious diagnosis, extra care is taken to assess whether the symptoms could be caused by an as yet unrecognised malignancy. Whilst there is limited evidence of specific malignancies that may be most prone to present in a similar way to PMR, we suggest consideration of prostate, haematological and lung cancers and lymphomas. Given the risk of cancer up to 12 months post PMR diagnosis, clinicians should maintain a high index of suspicion in PMR patients, especially in those who fail to respond to treatment or whose clinical appearance changes in some other way.

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