

The frequency of occult solid malignancy in patients with polymyalgia rheumatica-like symptoms

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Abstract

Aims: We aim to evaluate the clinical usefulness of systematic screening for occult cancer in patients with polymyalgia rheumatic (PMR)-like symptoms in real-life practice.

Methods: All patients seen by rheumatologists in Burgundy, France, between March 2016 and December 2018 for new-onset PMR that met the 2012 ACR/EULAR classification criteria were prospectively included. Patients underwent systematic screening including determination of the erythrocyte sedimentation rate, serum C-reactive protein levels, thoracic, abdominal and pelvic computed tomography (CT-TAP) and, in men, serum prostate-specific antigen. The standardized incidence ratio (SIR) for cancers was calculated using 2012 national estimates of cancer incidence. Potential predictive factors for the diagnosis of cancer were then evaluated using univariate and multivariate analyses.

Results: Among the 118 patients included, nine cases of cancer were confirmed and diagnosed with CT-TAP: kidney carcinoma ($n=4$), lung cancer ($n=2$), pancreatic, colon, and ampullary carcinoma ($n=1$ each). Among these cancers, five were localized (four kidney, and one ampullary carcinoma) and were treated with complete surgical resection. The expected incidence of cancer in the general population was 1.95, leading to an overall SIR of 4.6 (95% CI 2.4–8.9, $p < 0.0001$). An additional analysis was performed for the kidney carcinoma, and it showed a highly significant increase in SIR: 80.8 (95% CI 30.3–215.4). In 80% of patients, the PMR-like syndrome regressed during cancer treatment. No other predictive factors for cancer were found.

Conclusion: Systematic screening for cancer including CT-TAP in real-life practice revealed occult solid malignancy, mostly early-stage cancer, in a relevant proportion of patients presenting PMR-like symptoms. The high proportion of kidney cancer (40%) is worth highlighting, especially considering that it is not one of the most frequent cancers after 50 years of age.

Keywords: cancer, CT-scan, diagnosis, polymyalgia rheumatica, screening

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Polymyalgia rheumatica (PMR) is one of the most common inflammatory rheumatic diseases in the elderly population, with an annual incidence that varies from 12.7/100,000 to 50/100,000 in Europe.¹ PMR is an inflammatory disorder that causes shoulder and pelvic girdle pain and prolonged early morning stiffness in patients >50 years associated with a biological inflammatory syndrome.^{2,3}

PMR is often linked to giant cell arteritis, an inflammatory vasculitis affecting large vessels, and there is a considerable overlap between these two diseases. PMR-like symptoms have been described in association with other alternative diagnoses, in particular cancer. In some cases, PMR-like symptoms are related to a paraneoplastic syndrome. These cases typically have a poorer response to steroid treatment and the PMR symptoms most often regress

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quickly after complete removal of tumour cells.⁴ Some studies have reported finding no increase in the frequency of malignancies in patients with PMR.⁵⁻⁷ Conversely, some authors have suggested an increased prevalence of malignancy in patients with PMR-like symptoms.⁸⁻¹⁰ Ji *et al.*⁸ reported an increased risk of cancer with an overall standardized incidence ratio (SIR) of 1.19 after hospitalization. Similarly, Muller *et al.*⁹ reported an increased risk of malignancy in the first 6 months following a diagnosis of PMR [Hazard ratio: 1.69 (95% CI 1.18–2.42)]. However, because these studies were conducted in hospitals, and/or in large retrospective institutional databases, there is a potential source of selection bias. In addition, neither study evaluated what investigations should be performed to rule out malignancy, while it is well known that many of the investigations used to detect primary cancer are not effective in patients with cancer of unknown origin.^{11,12}

In real-life practice, thoracic, pelvic, and abdominal CT-scan (CT-TAP) is the most widely used imaging tool for finding occult cancer when suspected, but its value in patients presenting symptoms of PMR is not known. In the present study, standardized systematic screening was performed by rheumatologists in Burgundy (France) who were given an opportunity to investigate the association between PMR and occult malignancy.

Thus, the aim of the present study was to prospectively evaluate the prevalence of solid malignancy in patients presenting with symptoms of PMR and the relevance of a systematic screening for this population in a clinical setting.

Methods

All patients seen by a rheumatologist in their private practice between March 2016 and December 2018 for PMR-like symptoms consistent with the 2012 ACR/EULAR classification criteria for PMR³ were prospectively included. Patients with a previous history of cancer were not excluded. The following screening was systematically performed: determination of the erythrocyte sedimentation rate (ESR), serum C-reactive protein (CRP), CT-TAP with contrast agent and, in men, serum prostate-specific antigen (PSA).

The following variables were collected: age, gender, medical history, in particular past medical history of cancer, duration of PMR, reported symptoms, weight loss, body temperature,

results of physical examination, results of the standardized screening and of any other associated evaluations over the first year. According to French legislation and after examination of this protocol by the French regional ethics committee, this study was performed in accordance with the principles of good clinical practice and the need for ethics committee approval was waived. Written informed consent was obtained from all patients.

Statistical analyses

First, the observed number of confirmed cancer cases (i.e. diagnosed using the standardized screening and confirmed with histological examination) was compared with the expected number of cases in the general French population. The expected number was calculated by indirect standardization from national estimations of gender- and age-specific overall solid cancer incidence rates for 2012.¹³ This method was used to obtain the SIR, that is, the ratio of the observed cases in the study population to the expected numbers according to what should be observed in the general population of similar age and gender. A Poisson distribution was assumed for the observed number of cancers to calculate 95% confidence intervals (95% CI) and *p*-values for the SIRs.

Next, SIRs were calculated separately for men and women, for patients aged below or above the median age of the sample, for patients with and without a history of cancer, and for patients with disease duration above and below the median disease duration of the sample.

Univariate and multivariate analyses were then performed in order to evaluate the potential predictive factors for confirmed cancers that were diagnosed using the standardized evaluation. The variables of interest were age, gender, a history of cancer, disease duration, ESR and serum CRP levels. Proportions of categorical variables (gender and history of cancer) and means/medians of continuous variables (age, disease duration, ESR and CRP levels) were compared between patients with and without confirmed cancer using Fisher's exact test and analysis of variance/Kruskal–Wallis test, respectively.

A *p*-value of <0.05 was considered statistically significant. SAS 9.3 (SAS Institute Inc., Cary, North Carolina) was used for statistical analyses.

Results

In total, 118 patients fulfilling 2012 ACR/EULAR classification criteria for PMR were included: 68 women and 50 men, median age 73 years, median disease duration 10 weeks. Fifteen patients (13%) had cancer in their past medical history (four breast cancer, two each of prostate and non-melanoma skin cancer, and one each of kidney, kidney and prostate, tongue, cervical cancer, melanoma, lymphoma and myeloproliferative disorder). There were some missing data for PSA measurements ($n = 9$).

The results of the standardized evaluation are shown in Table 1. PSA levels were elevated in eight (19%) men. Subsequent evaluations including prostate biopsy ruled out cancer in seven patients and were not performed in one patient. CT-TAP showed an abnormal mass or adenopathy in 33 patients. In these patients, subsequent testing led to the diagnosis of histologically confirmed cancer in nine patients (four kidney carcinoma, two lung cancer, one each of pancreatic, colon, and ampullary carcinoma) and of possible or probable cancer in two patients. In all cases, the cancer was newly diagnosed and non-metastatic, and it was not a relapse of a prior malignancy. Interestingly, none of the data in the medical interview and/or physical examination would have led to a suspicion of occult malignancy. In three other patients, the systematic screening led to the diagnosis of possible cancer (mediastinal lymphadenopathy in one, a pelvic mass in another and elevated PSA in the third) but without confirmation by histological analysis since all patients declined further investigations and were lost to follow-up.

Among the nine confirmed cancers (Table 2), five were localized (four kidney and one ampullary carcinoma) and were treated with complete surgical resection. In these patients, the PMR syndrome regressed after cancer treatment. The patient diagnosed with pancreatic cancer and one diagnosed with lung cancer were treated with chemotherapy. The PMR-like syndrome regressed during treatment (chemotherapy or surgery) and oral steroids were not justified during follow-up. The patient diagnosed with colon cancer and one of the two with lung cancer died in the following months. None of the potential predictive factors for cancer (age, gender, cancer in the past medical history, disease duration, weight loss, ESR and serum CRP levels) was associated with a diagnosis

Table 1. Results of the standardized initial evaluation in 118 patients with PMR symptoms (according to 2012 ACR-EULAR criteria).

	Patients $n = 118$
ESR mean mm/hour (SD)	57.0 (31.3)
CRP mean mg/l (SD)	61.6 (44.3)
PSA*, n with increased result (%)	8 (19)
Thoracic abdominal and pelvic CT-scanning	
Suspected mass	33
Kidney	4
Lung	8
Pancreatic	1
Colon	1
Ampullary	1
Uterus	2
Adrenal glands	4
Ovary	1
Breast	1
Bladder	1
Adenopathy	7
Cancer confirmed, n (%)	9 (8)
Cancer not confirmed but highly suspected, n (%)	3 (2)
*Nine missing data (118 patients). CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; PSA, serum prostate-specific antigen.	

of confirmed cancer in univariate analysis in this cohort (Table 2).

The SIRs were calculated for the nine confirmed cancers diagnosed using the systematic screening. In the general population of France, the expected number of cancers was 1.95. The SIR was 4.63 (95% CI 2.41–8.89, $p < 0.001$) (Table 3). The SIRs were significantly increased in both men and women, in patients younger or older than 74 years, in patients with or without a past history of cancer, and in patients with disease duration of more or less than 8 weeks (Table 3). As four cases of kidney cancer were found, an additional analysis was performed for this particular solid malignancy, and it showed a highly significant increase in SIR: 80.8 (95% CI 30.3–215.4).

Table 2. Characteristics of the PMR-like symptoms patients with cancer (all confirmed by histological analysis) ($n=9$) compared with PMR patients without cancer ($n=109$).

	PMR-like symptoms patients with cancer ($n=9$)	PMR patients with no cancer ($n=109$)	p
Gender men n (%)	6 (67)	44 (40.4)	0.13
Age mean years (SD)	71.8 (7.5)	72.3 (9.2)	0.79
Cancer in past medical history n (%)	2 (22)	13 (11.9)	0.37
Duration onset mean weeks (SD)	12.8 (15.2)	11.6 (15.2)	0.91
Symptoms			
Bilateral shoulder pain/stiffness n (%)	9 (100)	100 (91.7)	0.37
Bilateral hip pain/stiffness n (%)	7 (78)	78 (71.6)	0.69
Stiffness >1 h n (%)	8 (89)	101 (92.7)	0.68
Depression and/or weight loss n (%)	2 (22)	17 (15.6)	0.60
ESR			
Mean mm/hour (SD)	54 (32)	57.7 (31.4)	0.84
ESR >40 mm/hour n (%)	5 (55)	75 (68.8)	0.37
CRP mean mg/l (SD)	70 (43)	60.8 (44.5)	0.47
Suspected cancer at questioning and/or physical examination	0	0	NA
Follow-up			
Regression of PMR syndrome after cancer treatment n (%)	7 (78)	NA	NA
Rapid death related to cancer n (%)	2 (20)	NA	NA
CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; NA, not applicable; PMR, polymyalgia rheumatica.			

Discussion

In the present study, the observed number of cancers in a population of patients presenting with PMR-like symptoms was much higher than expected in the general population of similar age and gender. Most of these solid tumours were discovered using systematic CT-TAP with contrast agent.

The present results raise several questions. Firstly, is a PMR-like syndrome associated with cancer in a relevant proportion of patients? This hypothesis has been put forward in previous studies^{9,14} whose results were interesting but potentially affected by a small sample size and/or from higher risks of bias than in the present study. Our results, which show a significant increase in the number of observed cancers compared with that expected in the general population, are in favour of this

hypothesis. Moreover, the follow-up of the patients suggests that the association was not coincidental, as in eight patients who were diagnosed with cancer and then treated, the PMR-like syndrome regressed during treatment. The high proportion of kidney cancer (40%) is worth highlighting, especially considering that it is not one of the most frequent cancers after 50 years of age.¹³ Musculoskeletal symptoms like PMR have not been described in the most common type of kidney cancer, in which unspecific symptoms like fatigue, fever or cachexia or endocrine involvement (hypercalcaemia, hypertension, polycythaemia) were not proportional to tumour size or metastatic spread.¹⁵

On the other hand, previous studies^{5,6} failed to demonstrate any increase in the frequency of cancer in patients suffering from PMR. The results of

Table 3. Standardized incidence ratio (SIR): ratio of the observed number of cancers in the PMR-like symptoms population to the expected number of cancer cases according to the national estimations of gender- and age-specific overall solid cancer incidence rates for 2012 (95% CI).

	Observed cancers (PMR population) <i>n</i>	Expected cancers <i>n</i>	SIR (95% CI)	<i>p</i> -value
All Cancers				
Whole sample	9	1.95	4.6 (2.4–8.9)	<0.001
Sex				
Men	6	1.16	5.2 (2.3–11.5)	<0.001
Women	3	0.78	3.8 (1.2–11.9)	0.020
Age				
≤74 years old	4	0.85	4.7 (1.8–12.6)	0.002
>74 years old	5	1.10	4.6 (1.90–11.0)	0.001
History of cancer				
No	7	1.68	4.2 (2.0–8.8)	0.001
Yes	2	0.26	7.8 (1.9–31.2)	0.0036
Duration of symptom (PMR)				
≤8 weeks	7	1.20	5.8 (2.8–12.2)	<0.001
>8 weeks	2	0.46	4.3 (1.1–17.3)	0.038
Kidney Cancer	4	0.05	80.8 (30.3–215.4)	<0.001

PMR, polymyalgia rheumatic; SIR, standardized incidence ratio.

large cohort studies about PMR and cancer,^{7–10} which used more accurate PMR diagnostic criteria with exclusion diagnosis and performed careful follow-up to monitor patient response to steroid treatment, have concluded that there is no relationship between PMR and malignancy. However, paraclinical investigations to eliminate cancer were either not systematically performed or they included explorations such as chest X-ray or abdominal ultrasound whose sensitivity is questionable. In the present study, the key investigation was indisputably the CT-TAP, which was not systematically performed in other studies. Our systematic use of CT-TAP might explain the discrepant results.

The second question concerns the patients in whom PMR investigations should be done to rule out solid cancer. Although not observed in the present study, it seems reasonable that patients with a past history of cancer or in whom cancer is

suspected from the medical interview and/or physical examination undergo some investigations. Our results suggest, however, that investigations should also be performed in all patients, as (i) a relevant number of occult cancers was discovered; (ii) in all cases, none of the data obtained during the medical interview and/or physical examination could have led to suspicion of malignancy; (iii) no predictive factors were identified; (iv) if the systematic screening had not been performed, the patients would have been diagnosed only with PMR and there would have been an increased risk of cancer progression; and (v) the screening was highly valuable in more than 50% patients, as it resulted in the detection of localized cancer which was treated with surgical resection.

The third question pertains to the most appropriate initial examination. Serum PSA led to the diagnosis of prostate cancer in one patient, which is consistent with what can be expected in the

general population.¹³ This question might not be specific to PMR, however, and might be linked to the debate on the usefulness of PSA dosage in the general population.¹⁶ On the contrary, systematic CT-TAP appears to be of great interest, resulting in the diagnosis of occult solid malignancies which would not have been detected otherwise. CT-TAP is easy to implement as a routine exam and in patients with metastasis of unknown origin, and it has demonstrated better accuracy than chest X-ray and abdominal ultrasound.^{11,12} This suggests that screening with CT-TAP could be systematically performed in all patients presenting with symptoms suggestive of PMR. Nevertheless, some types of solid cancer can be insufficiently detected on CT, including digestive or bladder tumours.

In some cases, fluorodeoxyglucose (FDG)-positron emission tomography (PET) may be useful for PMR diagnosis, in particular in the evaluation of steroid-resistant PMR patients, in order to rule out associated giant cell arteritis or other large-vessel vasculitis or to detect both occult malignancy and deep infectious diseases that are part of the spectrum of differential diagnosis.^{17–21} Moreover, it could be used in patients with renal failure or with iodinated contrast agent allergy. Nevertheless, FDG/PET is not feasible for all types of cancer and can misdiagnose kidney cancer, the most frequent cancer in our study, because of the kinetics of FDG. Its place in paraneoplastic PMR-like syndromes and its cost-effectiveness need to be investigated in further studies.

There are also some limitations in this study. Firstly, only 70% of the rheumatologists in Burgundy took part in the study, but it can be assumed that they are representative of the whole population of rheumatology private practice in this French region. Secondly, the PSA assay was omitted in some patients ($n=9$). However, the CT-TAP, which was the most relevant evaluation, was performed in all patients. In our protocol, CT imaging did not include cervical examination, so neck cancer or thyroid cancer may have been missed. Thirdly, it might have been preferable to compare the results of in the index population with the results of the same screening performed in age and sex-matched healthy controls. However, our statistical model appears to be efficient to detect significant difference between groups as demonstrated. Nevertheless, a case-control study including

patients and age- and sex-matched controls would be useful for confirmation.

Also, few studies have evaluated the association between PMR and haematological malignancy. In a Swedish cancer register, Askling *et al.*²² identified 42,676 cases with lymphoma (non-Hodgkin and Hodgkin lymphoma and chronic lymphocytic leukemia) and found that 153 patients had been diagnosed with PMR or giant cell arteritis in the year before lymphoma diagnosis. Nevertheless, no link was found between these conditions, with an odds ratio (OR) of 0.81 (95% CI: 0.67–0.98). Using an American cancer registry, Anderson *et al.*²³ reported no association between PMR and non-Hodgkin lymphoma [OR=0.9 (95% CI: 0.8–1.0)] or other non-Hodgkin lymphoma subtypes diffuse large B cell lymphoma [OR=0.9 (95% CI: 0.8–1.1)], T-cell non-Hodgkin [OR=1.2 (95% CI: 0.8–1.8)] or marginal zone lymphoma [OR=0.7 (95% CI: 0.4–1.1)]. On the contrary, Fallah *et al.* reported an association between PMR and non-Hodgkin lymphoma (SIR=1.4)²⁴ and Hodgkin lymphoma (SIR=2.2),²⁵ using data from a Swedish healthcare database.

All of these studies were conducted from national registries and found that the lymphoma appeared generally within 1 year of the diagnosis of PMR. However, our study was not designed for screening non-Hodgkin or Hodgkin lymphoma.

The present results might have important clinical implications. Indeed, the majority of studies have reported an increase in the incidence rate of cancer in the years after a diagnosis of PMR, and some of these studies implemented close follow-up that is not representative of real-life practice. Another major point is the corticosteroid resistance in case of paraneoplastic syndrome with PMR symptoms. Corticosteroid resistance should raise suspicions about the possibility of solid occult cancer, and indicate a need for further investigations, possibly with CT-TAP. Otherwise, another recent strategy in PMR treatment is to introduce immunosuppressive treatment such as methotrexate²⁶ or anti IL-6R monoclonal antibody,²⁷ which are contraindicated in patients with recent malignancy. These considerations reinforce the need to rule out cancer at PMR diagnosis. In future, larger case-control studies are warranted to confirm our results and to better identify potential predictive factors before recommending systematic screening with CT-TAP to detect occult malignancy in patients presenting PMR-like symptoms.

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Conflict of interest statement

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