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Polymyalgia Rheumatica and its Association with Cancer

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Abstract

Objective: Polymyalgia rheumatica (PMR) is a common rheumatologic disease in the elderly population. Studies on the relationship between PMR and cancer have yielded mixed results and have been limited by multiple factors. This study examined the association between PMR and development of cancer in a community cohort.

Methods: A population-based cohort of 359 patients with PMR diagnosed between 1/1/1970 and 12/31/1999 and followed to 12/31/2013 was assembled along with a comparison cohort of 357 subjects. Records of the PMR and comparator subjects were reviewed for details concerning diagnosis of cancer. The cumulative incidence of malignancy in patients with and without PMR, adjusted for the competing risk of death, was estimated and compared using methods of Gray. Cox proportional hazards models were used to assess the trends in malignancy over time.

Results: There was no significant difference in the prevalence of malignancy prior to PMR incidence date/index date between the two groups with prior malignancies in 41 (11%) of patients with PMR, and 50 (14%) of non-PMR subjects (p-value=0.31). As well, there was no difference in the cumulative incidence of malignancy at 10 years following PMR incidence between patients with PMR and non-PMR subjects (cumulative incidence at 10 years ± SE: PMR 13.8 ± 2.0, control 13.1 ± 2.0; p-value=0.89).

Conclusion: There is no increased risk of malignancy in patients who are diagnosed with PMR when compared to subjects without PMR in this population-based cohort.

Keywords: Polymyalgia rheumatic; Cancer

Introduction

Polymyalgia rheumatic (PMR) is a common inflammatory condition, with a female predominance, diagnosed most in the elderly, with an estimated incidence of 58.7 per 100,000 persons over the age of 50 years. The incidence of PMR increases with age, and as the population continues to mature in coming years these numbers are expected to grow [1].

The etiology of PMR is currently unknown and can often be difficult to distinguish from other inflammatory conditions, including rheumatoid arthritis, spondyloarthropathies, or metabolic and malignant disorders [2]. Some of these autoimmune disorders, including rheumatoid arthritis and systemic lupus erythematosus, have been found to be associated with certain forms of cancer [3,4]. In contrast, patients diagnosed with giant cell arteritis (GCA), a condition associated with PMR, have been found to have fewer malignancies prior to diagnosis of GCA when compared to controls, and certainly no increased risk for cancer [5]. The association between PMR and cancer is unclear, with previous studies yielding mixed results, from a 69% increase in the risk of cancer in the first 6 months after diagnosis of PMR to other studies finding no association [6-9].

The relationship between PMR and development of malignancy is uncertain. A confirmed positive association would suggest benefit from increased cancer screening in this population. The purpose of this study was to further investigate the possible association between PMR and development of cancer.

Materials and Methods

Study subjects

This study was conducted, with the approval of internal review boards from Olmsted Medical Center and Mayo Clinic, in the population of Olmsted County, Minnesota, USA. This population is well suited for longitudinal, population-based cohort studies of patients with PMR because comprehensive medical records for all residents seeking any medical care for over 60 consecutive years are available for review. The medical records linkage system of the Rochester Epidemiology Project (REP) allows access to the complete inpatient and outpatient records from all health care providers for the local population including Mayo Clinic and its affiliate hospitals, the Olmsted Medical Center and its affiliated community hospital, local nursing homes and local private practitioners. The potential of this data system for population based research studies have been previously described [10,11] and assures virtually complete clinical

information for all PMR and comparator subjects among Olmsted County, Minnesota residents.

For this study, a previously established cohort containing patients diagnosed with PMR between January 1, 1970 and December 31, 1999 and followed until death, migration or 12/31/2013 was utilized [12]. All patients were physician diagnosed. Inclusion required the fulfillment of the following 3 criteria: (1) age ≥ 50 years, (2) bilateral aching and morning stiffness (at least 30 minutes) persisting for at least 1 month involving at least 2 of the following areas: neck/torso, shoulders/proximal arms and hips/proximal thighs and (3) an erythrocyte sedimentation rate >40 mm/hr (Westergren method). Patients with response (definite improvement in symptoms within 24 hours) to low dose corticosteroid therapy (≤ 20 mg of prednisone per day) were also considered to have PMR. Other diseases that might explain symptoms, such as rheumatoid arthritis, were excluded. For each PMR subject, a comparator subject without PMR at the time of the patient's PMR diagnosis was selected and assigned an index date that corresponded to the PMR incidence date. Matching criteria were similar birth year (± 3 years), sex and length of medical history as the PMR subject.

Data collection

The records of the PMR patients and non-PMR comparator subjects were reviewed for details regarding diagnosis of cancer. Each cancer diagnosis was then cross-indexed with the Mayo Clinic Cancer Registry to assure complete case ascertainment. For each malignancy, the date of diagnosis, site and type of malignancy were collected.

Statistical methods

Descriptive statistics (means, proportions, etc.) were used to summarize the data for the PMR and non-PMR cohorts. The proportion of patients with malignancies prior to PMR incidence/index date was compared between the cohorts using chi-square tests.

The cumulative incidence of malignancy in patients with and without PMR adjusted for the competing risk of death was estimated and compared using Gray's test. These methods are similar to the Kaplan-Meier method with censoring of patients who are still alive at last followup. However, patients who died prior to experiencing malignancy were appropriately accounted for to avoid overestimation of the rate of occurrence of malignancy, which may have occurred if such subjects were simply censored at death. Patients with malignancy prior to PMR incidence/index date were excluded from these analyses.

Cox proportional hazards models were used to compare the rate of development of malignancy, both overall and by site, between patients with PMR and the non-PMR comparison cohort. These same models were also used to assess the trends in malignancy over time.

Results

This study initially included 364 patients diagnosed with PMR and 364 non-PMR comparator subjects. At the time of evaluation 12 of these individuals did not have research authorization, resulting in 359 patients in the PMR cohort and 357 subjects in the non-PMR comparison cohort. The individuals in these two comparison groups were similar in age (mean age in years ± SD: PMR 73.5 ± 8.5, non-PMR 73.3 ± 8.5), sex (PMR 66.6% female, non-PMR 66.9% female) and follow up time (mean follow up time in years ± SD: PMR 11.8 ± 6.7, non-PMR 10.7 ± 7.4).

There was no significant difference in the prevalence of malignancy prior to PMR incidence date/index date between the two groups, with prior malignancies in 41 (11%) of PMR patients and 50 (14%) of non-PMR subjects (p-value 0.31). Further evaluation, specifically examining solid and hematologic malignancies followed by specific individual malignancies (head/neck, gastric, pancreatic, lymphoma, leukemia, etc.) also showed no difference between the two groups (Table 1).

Malignancy Site	Malignancy events prior to PMR incidence/non-PMR index date (no.)	p-value comparing prior events*
Any Malignancy	41/50	0.31
Solid	39/49	0.26
Hematologic	2/1	1.00
Head/Neck	3/1	0.62
Gastric	0	-
Pancreatic	0	-
Liver	0	-
Colon/Rectal	5/5	1.0
Other digestive	1/0	1.0
Lung	1/2	0.62
Other thorax	0	-
Bone	0	-
Soft tissue	0/3	0.12

Skin	4/0	0.12
Breast (female only)	13/16	0.70
DCIS	0/1	0.56
Ovary (female only)	0	-
Other gynecologic (female only)	2/4	0.69
Prostate (male only)	9/13	0.38
Kidney	0/2	0.25
Bladder	3/6	0.34
Other genitourinary	0	-
Ophthalmologic	1/0	1.00
Central Nervous System	0/1	0.5
Lymphoma	0	-
Leukemia	2/1	1.00
Multiple myeloma	0	-
Myeloproliferative syndrome	0	-
Myelodysplastic syndrome	0	-
Other	0	-

Table 1: Prevalence of malignancy in PMR and non-PMR patients prior to PMR incidence/index date. *Fisher's exact test.

Following PMR incidence, evaluation of the cumulative incidence of malignancy at 10 years for patients with PMR and non-PMR subjects also showed no difference between the two groups (cumulative incidence at 10 years ±SE: PMR 13.8 ± 2.0, control 13.1 ± 2.0; p-value 0.89). Again, solid and hematologic as well as individual subtypes of cancer were analyzed separately and their incidence was found to be no different between the two groups (Table 2).

Malignancy Site	Number of events after incidence/index in PMR/non-PMR	Cumulative incidence at 10 years for PMR patients (± SE)	Cumulative incidence at 10 years for non-PMR subjects (± SE)	p- value**
Any Malignancy	66/62	13.8 ± 2.0	13.1 ± 2.0	0.89
Solid	64/ 6	13.1 ± 1.9	11.4 ± 1.8	0.58
Hematologic	5/5	1.2 ± 0.6	1.1 ± 0.6	0.99
Head/Neck	4/5	0.3 ± 0.3	1.2 ± 0.6	0.74
Gastric	0/4	0.0	0.6 ± 0.4	0.049
Pancreatic	2/1	0.6 ± 0.4	0.0	0.56
Liver	1/1	0.3 ± 0.3	0.0	0.99
Colon/Rectal	16/10	3.5 ± 1.0	1.2 ± 0.6	0.23
Other digestive	0/1	0.0	0.3 ± 0.3	0.32
Lung	11/13	2.0 ± 0.7	3.2 ± 0.9	0.63
Other thorax	0	0.0	0.0	-
Bone	0	0.0	0.0	-

Soft tissue	2/2	0.3 ± 0.3	0.6 ± 0.4	0.97
Skin	6/1	0.6 ± 0.4	1.2 ± 0.6	0.98
Breast (female only)	11/11	2.7 ± 1.1	2.7 ± 1.1	0.96
DCIS	1/1	0.3 ± 0.3	0.4 ± 0.4	0.98
Ovary (female only)	1/0	0.0	0.0	0.32
Other gynecologic (female only)	3/1	1.3 ± 0.7	0.0	0.33
Prostate (male only)	15/10	10.0 ± 2.9	6.8 ± 2.5	0.34
Kidney	2/1	0.0	0.3 ± 0.3	0.58
Bladder	3/4	0.6 ± 0.4	1.2 ± 0.6	0.67
Other genitourinary	0/3	0.0	0.6 ± 0.4	0.08
Ophthalmologic	0	0.0	0.0	-
Central Nervous System	0	0.0	0.0	-
Lymphoma	0/1	0.0	0.3 ± 0.3	0.31
Leukemia	5/4	1.1 ± 0.6	0.9 ± 0.5	0.74
Multiple myeloma	0	0.0	0.0	-
Myeloproliferative syndrome	0	0.0	0.0	-
Myelodysplastic syndrome	0	0.0	0.0	-
Other	0/4	0.0	0.9 ± 0.5	0.043

Table 2: Cumulative incidence rate of malignancy in PMR and non-PMR patients following diagnosis of PMR/index date.

Finally, time trends analyses revealed no evidence of a difference in the relative malignancy rates in PMR compared to non-PMR over calendar time (p=0.70) or throughout follow-up after PMR incidence/index date (p=0.85).

Discussion

In this population-based cohort study, there was no increased risk of malignancy in patients diagnosed with PMR when compared to subjects without PMR. This was found to be true both before the presentation of PMR as well as after diagnosis.

In recent years, a number of studies have found that the risk of cancer is increased in other rheumatologic conditions, specifically rheumatoid arthritis as well as systemic lupus erythematosus [3,4]. As PMR is a similar inflammatory condition, the risk of malignancy in this population has also recently been explored. There have been several reports of PMR and an association with cancer, with some suggesting PMR as a paraneoplastic phenomenon [7,13,14], while a number of other studies, including the current report, have shown no increased risk of malignancy with PMR [8,9].

A large administrative database study from Sweden, which included 35,918 patients with GCA and PMR, reported an increased risk of cancer within the first year of diagnosis of PMR. This study utilized the Swedish Hospital Discharge Register, in which diagnoses of PMR are based on coding and not confirmed by individual medical record review [7]. PMR can be difficult to accurately diagnose due to nonspecific symptoms, no definitive testing that can confirm the diagnosis and lack of established and accurate diagnostic criteria. The diagnosis of PMR is therefore clinical and relies upon the knowledge of individual medical providers [1].

A 2013 study conducted using the United Kingdom General Practice Research Database showed a 69% increased risk of malignancy in patients with PMR within the first 6 months of diagnosis. Patients in this study were also identified based on medical coding rather than review of the medical record; diagnosis was supported by the requirement that patients were required to have received at least two prescriptions for corticosteroids following their diagnosis of PMR. This added requirement may have improved the accuracy of PMR diagnosis in this study, however there was no data available regarding response to treatment. Surveillance bias may also have played a role in these results as patients diagnosed with PMR have been noted to have increased health care utilization compared to the general population, with possibly increased cancer detection related to more frequent contact with the healthcare system [6].

Finally, a more recent systematic review [15] summarized available studies investigating the link between PMR/GCA and cancer diagnosis. This ultimately included 6 studies with pooled statistical analysis revealing a 14% excess risk of malignancy in patients with GCA/PMR. The risk of malignancy appeared to be higher in the first 6-12 months after diagnosis. However, when sensitivity analysis was performed excluding one of the six studies due to potential selection bias, the pooled risk ratio decreased to 8% and did not achieve statistical significance. This study was limited by multiple factors, including publication and referral bias, and inclusion of patients with

GCA. The majority of the included studies had small sample sizes, referral bias, incomplete diagnostic and relevant clinical information, lack of adequate comparator groups and/or limited follow up time [6-9].

Our findings contradict recent reports in the literature suggesting an increased risk of malignancy in individuals diagnosed with PMR. Though completed using a smaller population, some of the important limitations in previous studies were addressed by our approach. Selection and referral bias were avoided with the population-based approach. A comparison cohort of subjects never diagnosed with PMR was carefully established to examine the cancer question. With the resources of the Rochester Epidemiology Project comprehensive medical records were available for each study subject and cross referencing with the Mayo Clinic Cancer Registry ensured that no malignancies were missed. Using the available complete medical records also allowed for confirmation of accurate diagnoses of PMR in study subjects, which is not possible when using coding alone. Finally, the study subjects in this case were followed for at least10 years after diagnosis of PMR with the timing of diagnosis of each malignancy evaluated.

Potential limitations to this study include the fact that the population of Olmsted County, Minnesota is predominantly white; though our findings should reflect the majority of patients with PMR seen in Western countries [16,17]. However, our sample size of patients with PMR was limited by the relatively small size of the Olmsted County population. Therefore, our study was underpowered to detect small increases (<1.5 fold increased risks) in malignancy rates in subjects with PMR compared to those without PMR, but larger, significant increases would have been detected. Finally, this study, like all others previously reported, did not include data for non-melanomatous skin cancer.

In conclusion, our findings reveal that the risk of developing cancer is no higher in individuals with PMR when compared to individuals not afflicted with this condition. In this study an attempt was made to avoid the limitations of previous studies examining this same question and as a result is more likely to represent the true relationship between PMR and cancer. Based on these results, we suggest that cancer screening of patients with PMR should be according to national guidelines for age and sex of the patient.

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