con il patrocinio di

CIPOMO

rete oncologica

APPROCCI INTERDISCIPLINARI IN REUMATOLOGIA

5ª edizione

REUMATOLOGIA E MALATTIE NEOPLASTICHE

Malattie reumatologiche a maggior rischio neoplastico: **Arterite gigantocellulare e polimialgia reumatica**

Sara Monti
Università di Pavia

PMR and cancer risk

Intern Med. 2010;49(15):1641-3. Epub 2010 Aug 2.

Polymyalgia rheumatica as the first presentation of metastatic lymphoma.

Kampitak T[1].

Clin Exp Rheumatol. 2010 Jan-Feb;28(1 Suppl 57):111-2.

A case of gastric cancer presenting as polymyalgia rheumatica.

Yasunaga Y, Miyashita T, Makiyama J, Koga T, Izumi Y, Kitazato A, Kobayashi S, Fujioka H, Matsumoto A, Ito M, Migita K.

Ann Hematol. 2010 Jan;89(1):111-2. doi: 10.1007/s00277-009-0779-6. Epub 2009 Jul 25.

Occult Hodgkin lymphoma presenting as polymyalgia rheumatica: value of [18F]-FDG positron emission tomography.

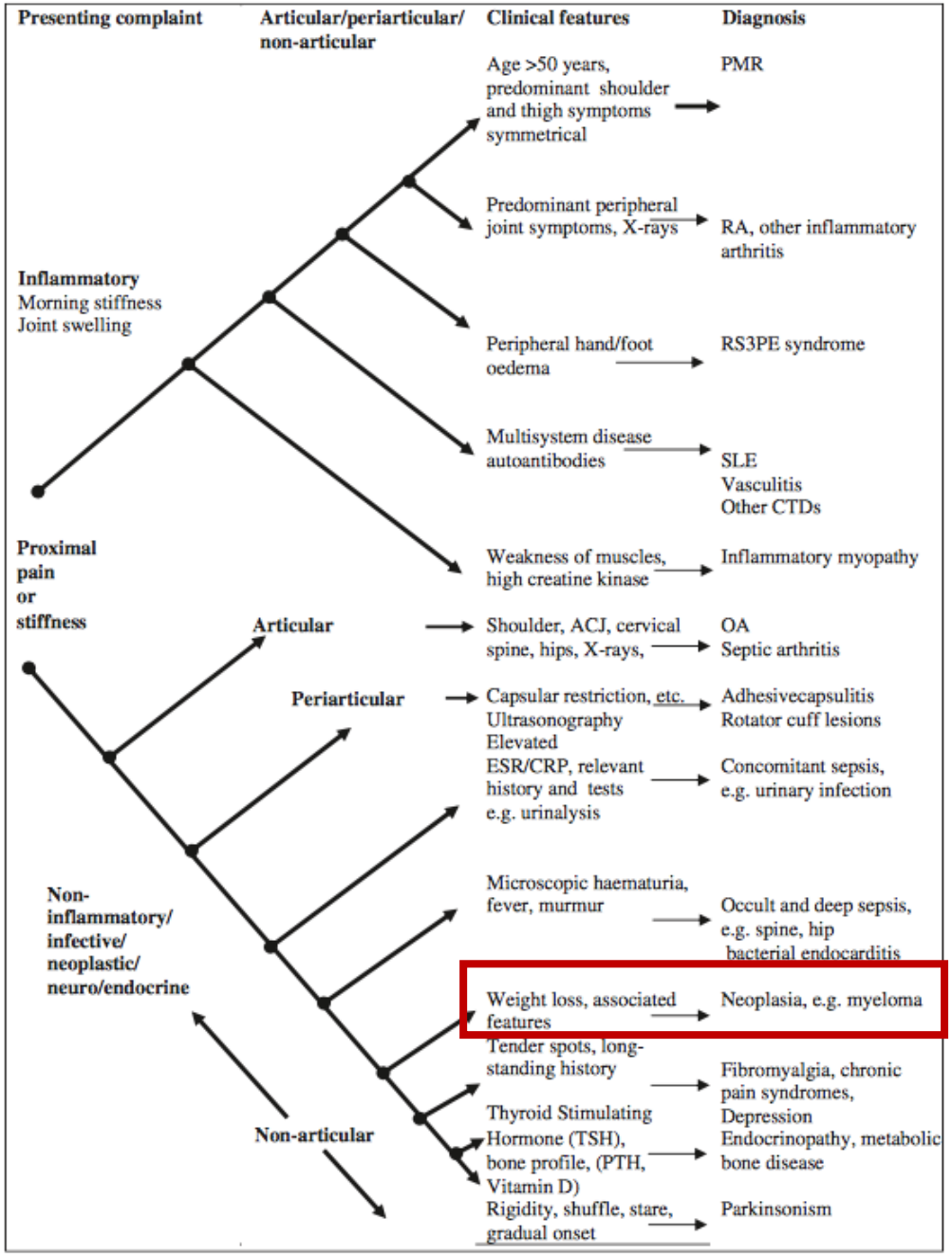
Durant C, Hervier B, Ansquer C, Masseau A, Hamidou M.

Case Rep Rheumatol. 2016;2016:2986297. doi: 10.1155/2016/2986297. Epub 2016 Aug 11.

Polymyalgia Rheumatica Revealing a Lymphoma: A Two-Case Report.

Verhoeven F[1], Guillot X[1], Chouk M[1], Prati C[1], Wendling D[1].

FIG. 1 Approach to the evaluation of proximal pain and stiffness. ACJ: acromio-clavicular joint.



BSR
The British Society for Rheumatology

BHPR
British Health Professionals in Rheumatology

BSR and BHPR guidelines for the management of polymyalgia rheumatica

Lab tests prior to steroids:

- Full blood count
- ESR
- CRP
- Plasma viscosity
- Urea and Electrolytes
- Liver function tests
- Calcium, alkaline phosphatase
- Protein electrophoresis / Bence Jones protein
- Thyroid stimulating hormone
- Creatine kinase
- RF
- ANA
- Chest X-ray (e.g. in cases with prominent systemic symptoms)
- Dipstick urinalysis

Step 1 Inclusion

Bilateral shoulder and/or pelvic girdle pain
Morning stiffness >45 min
Abrupt onset
Age >50 years
Duration >2 weeks
Acute-phase response (raised ESR/CRP)

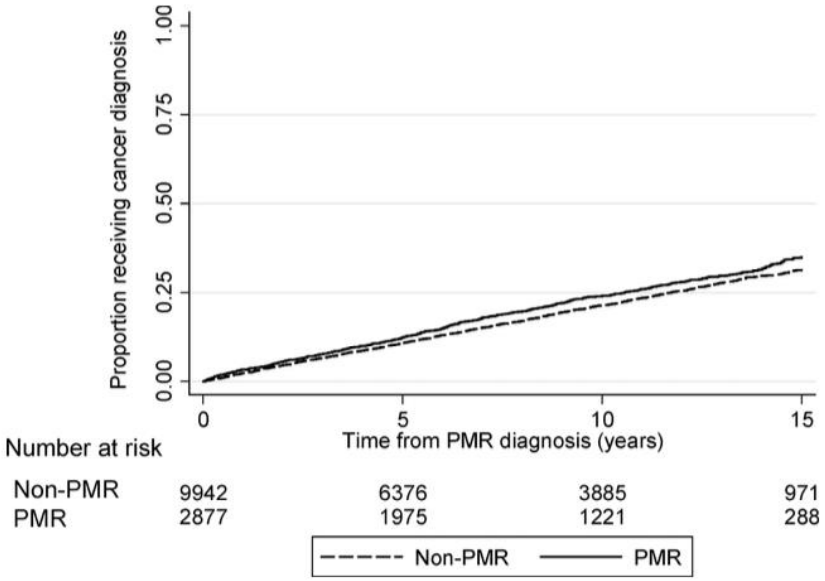
Step 2 Exclusion

Active cancer
Infection
Active GCA (see BSR Guidelines for GCA)
Inflammatory:
RA other arthropathies
SLE, myopathies, other CTDs
Non-inflammatory:
Local shoulder and hip conditions
Fibromyalgia/pain syndromes

Is cancer associated with polymyalgia rheumatica? A cohort study in the General Practice Research Database

Sara Muller, Samantha L Hider, John Belcher, Toby Helliwell, Christian D Mallen

Ann Rheum Dis 2014



Median follow-up time was 7.8 years (IQR 3.4, 12.3).

667 (23.2%) people with a PMR diagnosis developed cancer **compared with 1938 (19.5%) of those without PMR.**

In the first 6 months after diagnosis, those with a PMR diagnosis were significantly more likely to receive a cancer diagnosis (adjusted HR (95% CI): 1.69 (1.18 to 2.42)). The number of events was small, but occurrences of prostate, blood, lymph nodes, female reproductive and nervous system cancers may be more common in those with PMR in the first 6 months after PMR diagnosis.

Table 2 Association between PMR exposure and all cancer diagnoses, by time period

	Cancer diagnoses per 1000 person years		HR (95% CI)	
	PMR	No PMR	Unadjusted	Adjusted*
0–6 months (n=159)	38.9 (29.9 to 50.7)	21.4 (17.6 to 25.9)	1.82 (1.31 to 2.52)	1.69 (1.18 to 2.42)
6–12 months (n=154)	27.9 (20.3 to 38.3)	25.0 (20.8 to 29.3)	1.12 (0.78 to 1.61)	1.03 (0.70 to 1.51)
1–2 years (n=263)	23.6 (18.4 to 30.3)	23.2 (20.2 to 26.6)	1.02 (0.76 to 1.35)	1.04 (0.77 to 1.40)
2–5 years (n=559)	24.6 (21.1 to 28.7)	22.0 (20.6 to 24.5)	1.10 (0.92 to 1.31)	1.04 (0.86 to1.26)
5–10 years (n=866)	29.0 (25.5 to 33.0)	25.2 (23.3 to 27.2)	1.15 (0.99 to 1.34)	1.11 (0.95 to 1.30)
>10 years (n=504)	28.8 (24.1 to 34.4)	27.9 (25.3 to 30.9)	1.03 (0.84 to 1.27)	1.00 (0.82 to 1.23)

*Adjusted for age, gender and smoking status.

Association between rheumatic diseases and cancer: results from a clinical practice cohort study

Mattia Bellan[1,2] · Enrico Boggio[1] · Daniele Sola[1,2] · Antonello Gibbin[1,2] · Alessandro Gualerzi[1,2] · Serena Favretto[1,2] · Giulia Guaschino[1,2] · Ramona Bonometti[1,2] · Roberta Pedrazzoli[2] · Mario Pirisi[1,2,3] · Pier Paolo Sainaghi[2,3]

N = **1750 patients**, including N = 100 with PMR. A rheumatic disease was deemed paraneoplastic if cancer had been diagnosed in the 2 years preceding or following its onset.

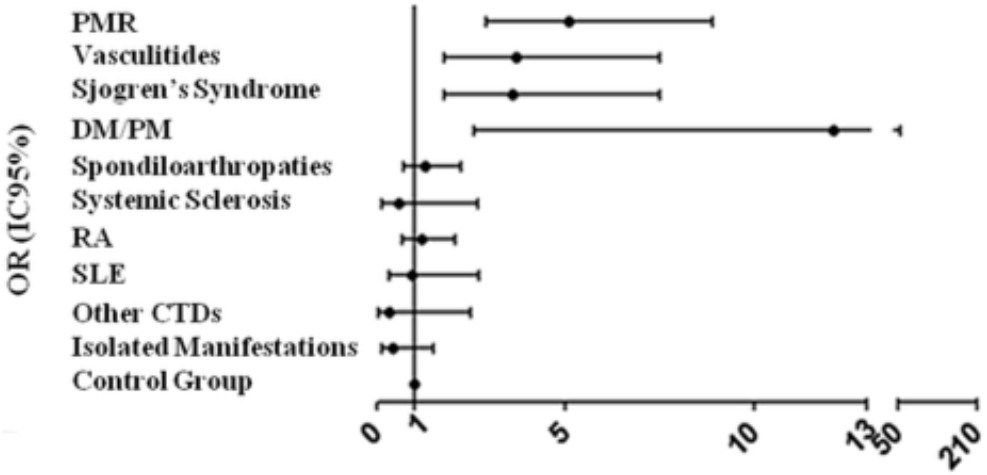


Table 4 Multivariate logistic regression analysis on potential paraneoplastic PMR predictors

	OR	95% CI	*p*
Tender joints ≥6	5.62	1.17–27.04	0.031
Male sex	3.73	1.15–12.04	0.028
Age >75 years	3.67	1.10–12.28	0.035
Weight loss ≥5 kg	2.37	0.59–9.44	0.221
Fever	0.21	0.02–2.15	0.188

χ^2 22.84, DF 5, $p < 0.0004$

Neoplastic disease	Number of patients	Percentage
Breast cancer	29	20.4
Colorectal adenocarcinoma	17	12.0
LH and LNH	17	12.0
Bladder cancer	11	7.8
Multiple myeloma	9	6.3
Chronic myeloproliferative and myelodysplastic syndromes	8	5.7
Lung cancer (SCLC e NSCLC)	7	4.9
Thyroid cancer	7	4.9
Endometrial cancer	6	4.2
Renal cancer	5	3.5
Prostatic adenocarcinoma	5	3.5
Other solid neoplasms	21	14.8
Total	142	100.0

"Other solid neoplasms" is a diagnostic category collecting all those syndromes diagnosed in less than three patients

Intern Emerg Med (2017) 12:621–627

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Rheumatology (Sunnyvale). 2015 ; Suppl 6: . doi:10.4172/2161-1149.S6-003.

Polymyalgia Rheumatica and its Association with Cancer

Emily C Pfeifer, MD[1], **Cynthia S Crowson, MS**[2,3], **Brittny T Major, MS**[2], and **Eric L Matteson, MD, MPH**[3,4]

[1]Department of Internal Medicine, Mayo Clinic, Rochester, MN, United States

- A population-based cohort of 359 patients with PMR
- comparison cohort of 357 subjects

Malignancy Site	Malignancy events prior to PMR incidence/non-PMR index date (no.)	p-value comparing prior events*
Any Malignancy	41 / 50	0.31

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

- **Prevalence previous malignancies** in 41 (11%) in PMR, and 50 (14%) in non-PMR (p=0.31).
- **Cumulative incidence of malignancy at 10 years** ± SE: PMR 13.8 ± 2.0, control 13.1 ± 2.0; (p=0.89)

Risk of malignancy in patients with giant cell arteritis and polymyalgia rheumatica: A systematic review and meta-analysis

Patompong Ungprasert, MD[a,b,*], Anawin Sanguankeo, MD[c], Sikarin Upala, MD[c], Eric L. Knight, MD, MPH[a]

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI	Year
Haga et al.	0.03	0.197	3.5%	1.03 [0.70, 1.52]	1993
Myklebust et al.	-0.15	0.194	3.6%	0.86 [0.59, 1.26]	2002
Kermani et al.	0.231	0.189	3.7%	1.26 [0.87, 1.82]	2010
Hill et al.	0.182	0.176	4.3%	1.20 [0.85, 1.69]	2010
Ji et al.	0.174	0.017	52.8%	1.19 [1.15, 1.23]	2010
Muller et al.	0.073	0.045	32.1%	1.08 [0.98, 1.17]	2013
Total (95% CI)			100.0%	1.14 [1.05, 1.22]	

Heterogeneity: Tau² = 0.00; Chi² = 7.56, df = 5 (P = 0.18); I² = 34%
Test for overall effect: Z = 3.38 (P = 0.0007)

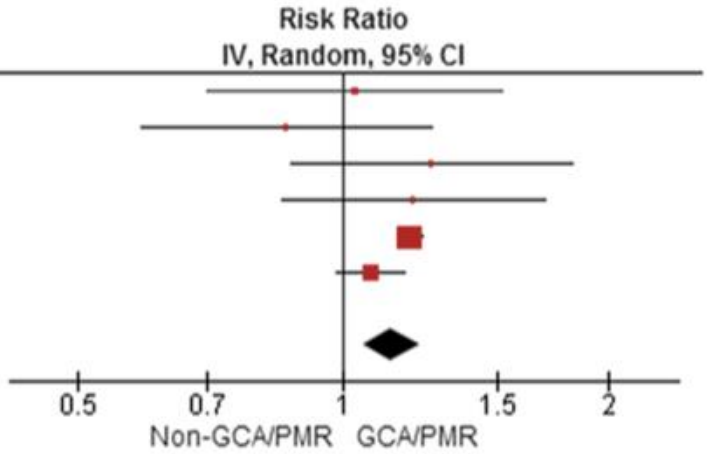


Fig. 2. A forest plot of overall malignancy risk.

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI	Year
Ji et al.	0.815	0.036	81.5%	2.26 [2.11, 2.42]	2010
Kermani et al.	0.854	0.505	2.5%	2.35 [0.87, 6.32]	2010
Muller et al.	0.525	0.183	16.0%	1.69 [1.18, 2.42]	2013
Total (95% CI)			100.0%	2.16 [1.85, 2.53]	

Heterogeneity: Tau² = 0.01; Chi² = 2.43, df = 2 (P = 0.30); I² = 18%
Test for overall effect: Z = 9.61 (P < 0.00001)

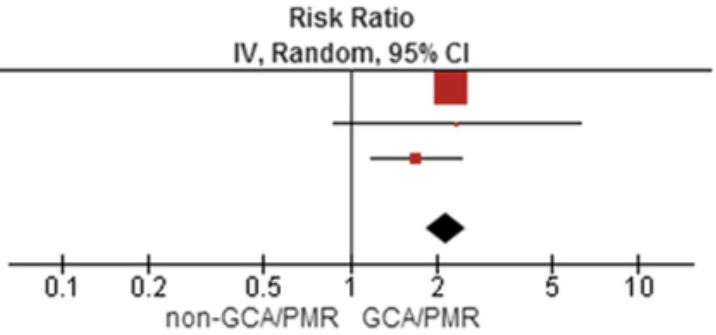


Fig. 3. A forest plot of malignancy risk in the first 6–12 months.

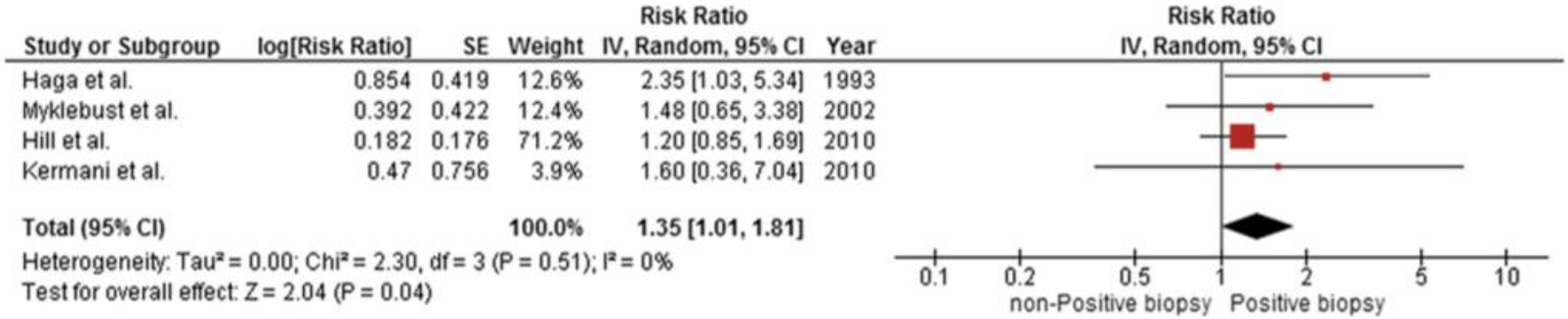


Fig. 4. A forest plot of malignancy risk in patients with a positive temporal artery biopsy.

We also performed a sensitivity analysis excluding the study by Ji et al., as this study included only patients with GCA/PMR who were admitted to a hospital, leading to a **potential selection bias** due to inclusion of only the most severe cases. **Exclusion of this study considerably altered the result of this meta-analysis as the overall pooled risk ratio dropped to 1.08 and did not achieve statistical significance (95% CI: 0.99–1.17)**, compared to 1.14 (95% CI: 1.05–1.23) in the complete analysis. The pooled risk ratio of cancer in the first 6–12 months also dropped to 1.76 (95% CI: 1.25–2.46) from 2.16 (95% CI: 1.85–2.53).

Seminars in Arthritis and Rheumatism 2014

Conditions mimicking polymyalgia rheumatica

Federico Ceccato,[a] Claudia Uña,[b] Mónica Regidor,[c] Oscar Rillo,[b] Silvia Babini,[c] Sergio Paira[a,*]

Neoplasms	n=4	
Lymphoma	1	Inguinal lymphadenopathy, persistently high ESR
Breast	1	Lack of response to steroids, ESR that decreases little with steroids
Pancreas	1	Fever, unexplained weight loss
Lung	1	Lack of response to steroids. History of smoking for 30 years. Lung CT
Rheumatic diseases	n=4	
Systemic lupus erythematosus	1	Vasculitis, high titre ANA, anti-DNA (+), polyarthritis
	1	46, leucopenia, widespread pain, polyarthritis
Sjögren's syndrome	1	Sicca symptoms, arthritis, ANA, ENA and RF (+), salivary gland biopsy (+)
		Lack of response to steroids, dactylitis, skin psoriasis
Psoriatic arthropathy	1	
Other diseases	n=8	
Hypothyroidism	1	Lack of response to steroids, high TSH
Cervical spinal stenosis	1	Partial response to steroids, paresthesias and loss of unilateral force
Infective endocarditis,	1	Murmur, fever, impaired general condition, leukocytosis, blood cultures (+)
Parkinson's disease	1	Resting tremor, lack of response to steroids and good response to antiparkinsonian treatment
Statin myalgia	1	Lack of response to steroids, good response to atorvastatin suspension
CPPD crystal disease	2	Crown syndrome, radiographic CPPD and C1-C2 CT
Vitamin D deficiency	1	Lack of response to steroids, ↓ vitamin D count

Rheumatol clin 2011

Patients had a diagnosis of PMR if they met the following criteria: age≥50 years, erythrocyte sedimentation rate (ESR) at the time of diagnosis>40 mm, persistent pain and stiffness of at least one mon- th of evolution in two of the following areas: neck, shoulders or proximal arms, hips or proximal lower limbs.

Results: Sixteen of the 200 patients **(8%) had other diseases during follow up.**

- Malignancies (n=4), rheumatic diseases (n=4) were the most common entities,

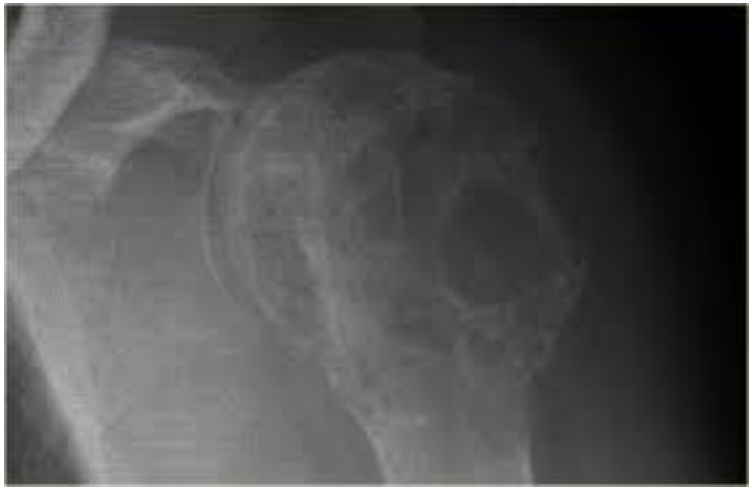
The average length change of diagnosis was 4.5±3 months.

Ten patients had **no response to steroids and two had persistently elevated ESR.**

Case Report

Metastatic Prostate Cancer Mimicking Polymyalgia Rheumatica

Case Rep Emerg Med 2011



J Clin Rheumatol. 1996 Dec;2(6):305-8.

A polymyalgia rheumatica-like syndrome as presentation of metastatic cancer.

Naschitz JE[1], Slobodin G, Yeshurun D, Rozenbaum M, Rosner I.

GCA and cancer risk

Risk of cancer in patients with biopsy-proven giant cell arteritis

Catherine L. Hill[1], Antonia Cole[1], Maureen Rischmueller[1], Thomas Dodd[2], Mark Coleman[3], Graeme Tucker[4] and Peter Roberts-Thomson[5]

	Total		
	Observed	Expected	SIR (95% CI)
All cancer sites (140–208)	31	25.83	1.2 (0.8, 1.6)
Colorectal (153–4)	5	4.55	1.1 (0.4, 2.5)
Lung (162)	2	3.33	0.6 (0.2, 2.8)
Breast (174)			
Prostate (185)			
Bladder (188)	2	1	2.0 (0.2, 7.3)
Other[a]	14	12.72	1.1 (0.6, 1.9)

Rheumatology key message

- We did not find evidence of an association between cancer and biopsy-proven GCA in this population.

Rheumatology 2010

Cancer in Biopsy-Proven Giant Cell Arteritis. A Population-Based Study

Miguel A. Gonzalez-Gay, MD, PhD,* Maria J. Lopez-Diaz, MD,*
Luciana Martinez-Lado, MD,* Jose L. Peña-Sagredo, MD, PhD,‡
Hugo Lopez-Agreda, MD,* Jose A. Miranda-Filloy, MD,*
Carlos Gonzalez-Juanatey, MD, PhD,† Amalia Sanchez-Andrade, MD,
Javier Martin, MD, PhD,§ and Javier Llorca, MD, PhD¶

Table 3 Occurrence of Cancer in 255 Biopsy-Proven GCA Patients

	N (%)*	Age (y) at the Time of GCA (Mean ± SD)	Age (y) at the Time of Cancer (Mean ± SD)	Type of Tumor: Solid N (%)†	Type of Tumor: Hematological N (%)†
Before the diagnosis of GCA	9 (22.5)	79.9 ± 5.5	75.4 ± 6.4	9 (100)	0 (0)
At the time of diagnosis of GCA	1 (2.5)	73.0	73.0	0 (0)	1 (100)
After the diagnosis of GCA	30 (75)	73.5 ± 6.5	79.4 ± 6.4	25 (83)	5 (17)

*Based on the total number of cancers (n = 40) observed in this series.
†Based on the total number of cases observed in each specific time period.

Table 5 Differences Between Biopsy-Proven GCA Patients who Developed Cancer and the Remaining Biopsy-Proven GCA Patients

Variable	Cancer: Yes (N = 39) (15.3%)	Cancer: No (N = 216) (84.7%)	P
Age (y) at diagnosis (mean ± SD)	74.8 ± 6.7	75.1 ± 6.9	0.81
Women	19 (48.7)	119 (55.1)	0.46
Delay to diagnosis (wk) (mean± SD)*	10.5 ± 9.6	10.2 ± 11.2	0.87
Scalp tenderness	19 (48.7)	66 (30.6)	0.03
Constitutional syndrome†	25 (64.1)	128 (59.3)	0.57
Headache	35 (89.7)	180 (83.3)	0.31
Abnormal temporal arteries‡	35 (89.7)	148 (68.5)	0.01
Jaw claudication	12 (30.8)	90 (41.7)	0.20
Dysphagia	4 (10.3)	8 (3.7)	0.09
Polymyalgia rheumatica	15 (38.5)	86 (39.8)	0.87
Fever (temperature ≥38°C)	5 (12.8)	22 (10.2)	0.62
Visual manifestations	9 (23.1)	48 (22.2)	0.91
Permanent visual loss	3 (7.7)	29 (13.4)	0.44
Cerebrovascular accidents	1 (2.6)	5 (2.3)	1.00
Limb claudication of recent onset	1 (2.6)	5 (2.3)	1.00
ESR (mean ± SD) mm/1st h§	93.5 ± 20.3	93.9 ± 23.0	0.91
Hemoglobin (mean ± SD) g/dL§	11.4 ± 1.5	11.8 ± 1.7	0.17
Platelet count/mm^3 (mean ±SD)§	390,000 ± 121,000	410,000 ± 137,000	0.39
Raised ALP§¶	10 (25.6)	51 (23.6)	0.78

The results from this series do not support an overall increase of mortality due to cancer in GCA.

Semin Arthritis Rheum 2007

Cancer Preceding Giant Cell Arteritis: A Case-Control Study

Arthritis Rheum. 2010 June ; 62(6): 1763–1769. doi:10.1002/art.27429.

We identified **204 GCA** cases and **407 controls**.
At index date, **45 (22%) GCA patients and 125 (31%) non-GCA patients had a previous cancer (**p=0.022).

Cancer prior to diagnosis of GCA or index date

Variable	Cases		Controls		OR* (95% CI)	P-value
	N	%	N	%		
Any malignancy before index date	45	22	125	31	0.63 (0.42, 0.94)	0.022
Any malignancy 1 year before index date	7	3.4	11	2.7	1.25 (0.47, 3.30)	0.65
Any malignancy other than non-melanoma skin cancer before index date	23	11	85	21	0.48 (0.29, 0.79)	0.004
Any malignancy excluding non-melanoma skin cancer 1 year before index date	2	1.0	6	1.5	0.65 (0.13, 3.25)	0.60
Any cancer excluding non-melanoma skin cancer before index date**						
Male	6	15	15	18	0.75 (0.26, 2.14)	0.59
Female	17	10	70	22	0.42 (0.24, 0.75)	0.003
Age <75 years	9	10	36	20	0.46 (0.21, 1.01)	0.052
Age ≥75 years	14	12	49	22	0.49 (0.26, 0.94)	0.031

In this population-based case-control study, GCA patients had significantly fewer malignancies prior to index date compared to controls.

Fever of Unknown Origin in Older Adults

Clin Geriatr Med 23 (2007) 649–668

Diagnoses	Elderly (n = 47)
Infections	12 (25.5%)
Abscess	2
Endocarditis	1
Tuberculosis	6
Viral infections	1
Multisystem disease	15 (31.9%)
Tumors	6 (12.8%)
Miscellaneous	5 (10.6%)
Drug-related fever	3 (6.4%)
Habitual hyperthermia	0
Factitious	0
No diagnosis	6 (12.8%)

CASE REPORT Open Access

Migratory large vessel vasculitis preceding acute myeloid leukemia: a case report

Dinusha Chandratilleke[1,2*], Anthea Anantharajah[1], Mauro Vicaretti[3], Warwick Benson[4] and Lucinda J. Berglund[1,2]

In the literature, there have been case reports of large vessel vasculitis occurring in individuals with myelo- dysplastic syndrome (MDS), some of whom have later developed acute myeloid leukemia (AML).

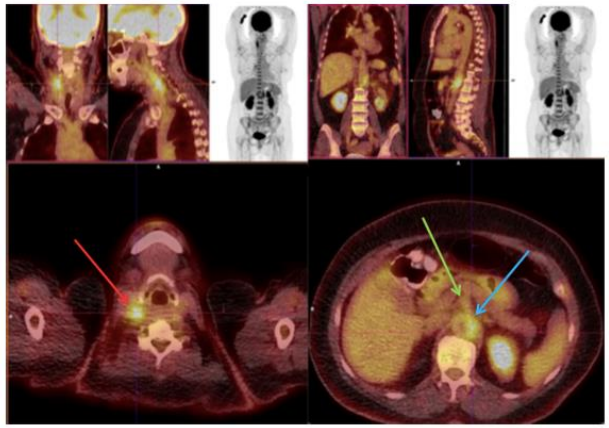


Fig. 3 Positron emission tomography scan demonstrating diffuse, intense fluorodeoxyglucose uptake of the right common carotid artery (*red arrow*), abdominal aorta (*blue arrow*), and superior mesenteric artery (*green arrow*)

Intern Med. 2016;55(3):289-93. doi: 10.2169/internalmedicine.55.5164. Epub 2016 Feb 1.

Acute Myeloid Leukemia Complicated by Giant Cell Arteritis.

Tsunemine H[1], Umeda R, Nohda Y, Sakane E, Akasaka H, Itoh K, Izumi M, Tsuji G, Kodaka T, Itoh T, Takahashi T.

Otolaryngol Head Neck Surg. 2015 Jan;152(1):187-8. doi: 10.1177/0194599814555856. Epub 2014 Oct 31.

Perivascular marginal zone lymphoma mimicking temporal arteritis.

Linxweiler M[1], Hasenfus A[2], Wolf G[3], Schick B[3].

A 73-year-old female was referred to our clinic with a chief complaint of **left-sided temporal swelling accompanied by occasional frontotemporal headaches, jaw claudication, and vertigo** for 3 months. **Normal CRP and ESR!**

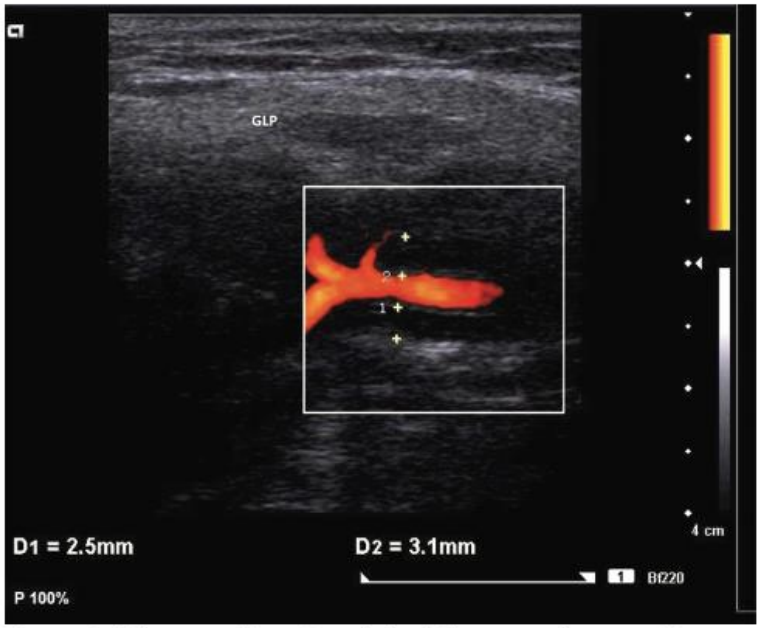


Figure 1. Ultrasound imaging of the left temporal artery demonstrating a markedly thickened vessel wall measuring 2.5 mm and 3.1 mm.

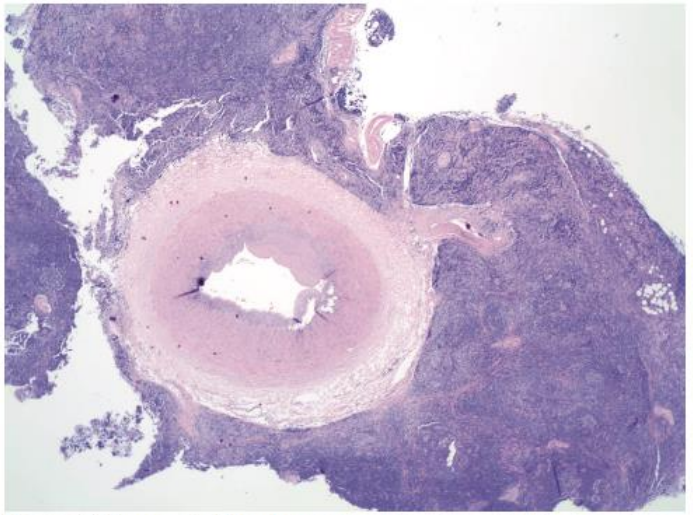


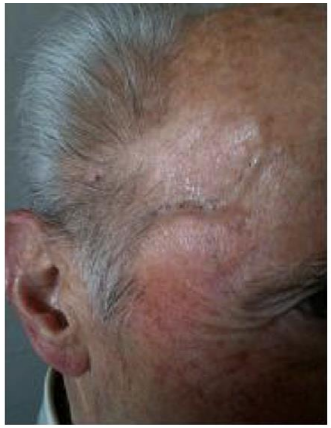
Figure 2. Segment of the left temporal artery showing an extensive perivascular lymphoid infiltrate (Giemsa stain, 2× magnification).

Joint Bone Spine. 2012 Mar;79(2):195-7. doi: 10.1016/j.jbspin.2011.09.007. Epub 2011 Dec 28.

AL amyloidosis with temporal artery involvement simulates giant-cell arteritis.

Audemard A[1], Boutemy J, Galateau-Salle F, Macro M, Bienvenu B.

6- month history of weight loss, weakness, and decreased appetite. **Bilateral jaw claudication, bi-temporal headache, myalgia, arthralgia of his shoulder, and acral paresthesia. The temporal arteries were noted to be prominent (Fig. 1), with tenderness on palpation and decreased pulsation**. The patient presented with macroglossia, buccal dryness, and acral hypoesthesia with areflexia. Results from a complete blood-cell count, renal function, **C-reactive protein,** and calcium levels were all **within normal ranges**. Ultrasonographic evaluation of the temporal artery revealed a "**halo sign**" suggestive of GCA.



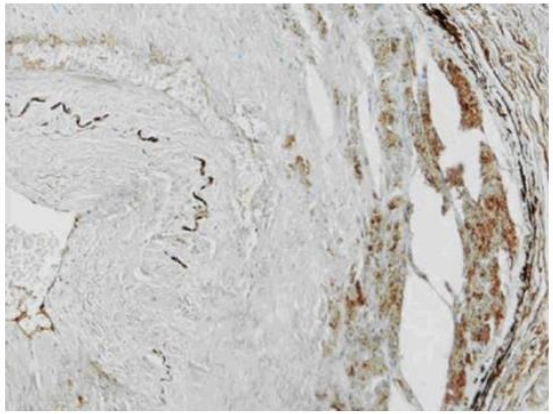
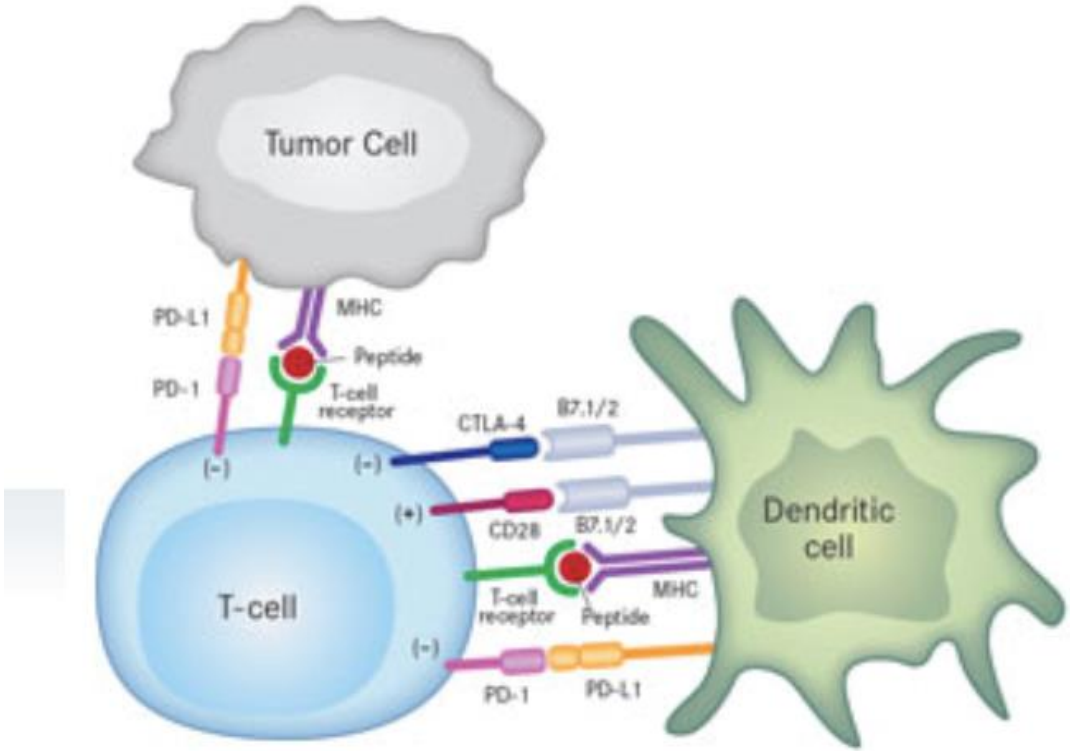


Fig. 3. Kappa-positive amyloid deposits.

PMR, GCA and cancer risk: the other way around?!



Nivolumab Causing a Polymyalgia Rheumatica in a Patient With a Squamous Non–Small Cell Lung Cancer

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We report a case of PMR in our patient during treatment with nivolumab for advanced squamous NSCLC. Our patient's symptoms match with the classical clinical presentation of PMR[6]: age > 50 years, a debilitating pain in the lumbar vertebrae, elbow, shoulder, and hips with morning stiffness expressed after about 7 months of treatment. Our case is among the 50% of PMR cases that also present distal manifestations, with wrist and metacarpophalangeal synovitis.[7] This symptomatology was associated with an inflammatory syndrome. Infectious disease, cancer progression, bone metastasis, and other rheumatic disorders were excluded.

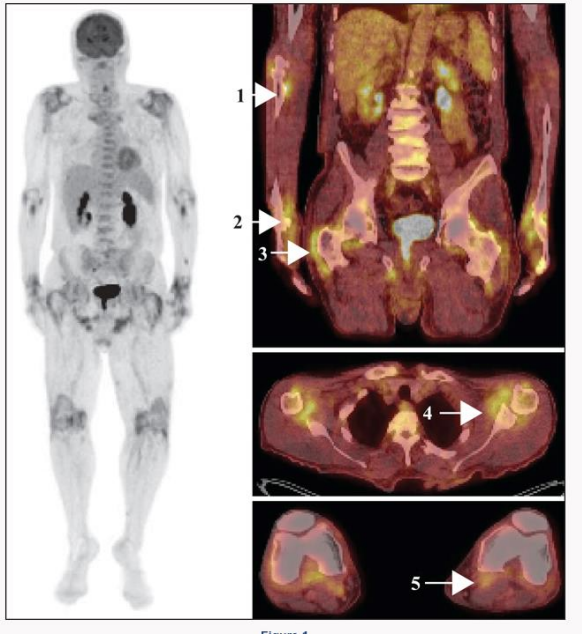
Polyarthritis or arthralgia has been described in around 5% of patients with immune checkpoint blockade.[8] In the literature, the occurrence of PMR associated with giant cell arteritis is described in 2 patients with metastatic melanoma who were treated with ipilimumab (an immune checkpoint inhibitor targeting CTLA-4).[9] The first patient had received 5 treatment cycles, when he developed an occipital headache, scalp tenderness, jaw claudication, shoulder and neck myalgia, and transient diplopia. The second patient presented arthralgia, trismus, left-sided facial swelling, and morning stiffness in his proximal shoulders' joints after 4 cycles of ipilimumab. In these 2 cases, the improvement of clinical symptoms due to corticosteroid therapy is consistent with our report. PMR was also reported in 2 patients treated with pembrolizumab. One occurred after 2 weeks of pembrolizumab and was treated initially by prednisone 25 mg, then 10 mg, and after

Eur J Dermatol. 2016 Oct 1;26(5):513-514.

Polymyalgia rheumatica occurring during treatment with ipilimumab.

Maniu C[1], Kobe C[2], Schlaak M[1], Mauch C[1], Eming SA[1].

Eur J Dermatol. 2016 Oct 1;26(5):513-514.



Arthritis Rheumatol. 2014 Mar;66(3):768-9. doi: 10.1002/art.38282.

Drug-associated polymyalgia rheumatica/giant cell arteritis occurring in two patients after treatment with ipilimumab, an antagonist of ctla-4.

Goldstein BL[1], Gedmintas L, Todd DJ.

Take home messages

- PMR is associated with a slightly increased risk of cancer, particularly early after the onset of the disease
- In a patient with PMR symptoms cancer should always be ruled out
- PMR can be misdiagnosed in cases of metastatic cancer
- GCA is not associated with an increase in the risk of malignancies or cancer-related mortality
- A possible exeption is acute myeloid leukemia
- Also in this case cancer can mimick the rheumatologic disease

Always keep a high level of suspicion in cases that are not clinically typical and that do not respond to treatment as expected

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