Clinical implications of fever at diagnosis in polymyalgia rheumatica: an age- and sex-matched case control study of 120 patients

Sirs,

Polymyalgia rheumatica (PMR) is a common inflammatory disorder that typically occurs in patients over 50 years of age. PMR can be found as an isolated phenomenon or in association with giant cell arteritis (GCA) (1, 2). Although markers of inflammation are often raised, fever is reported in only 10% of PMR patients (3, 4). Large-vessel FDG uptake can be observed in 15% of PMR patients (5). As fever is common in GCA, it could be indicative of subclinical large-vessel vasculitis in PMR that may be visualised with FDG PET.

Patients with newly diagnosed PMR were identified from a local registry of the period 2000-2019. Diagnosis was based on the judgement of an experienced clinician (DB and SV) after a 6-month follow-up, taking into account all information (clinical data and evolution, laboratory and imaging results). For each PMR patient with fever (PMR_F) at diagnosis, two PMR patients without fever (PMR_{NF}) were randomly identified and matched to age (±2 years) and sex. We excluded patients with signs or symptoms of GCA. This study was approved by the Ethical Committee research UZ/KU Leuven. Informed consent was waived because of the retrospective nature and anonymised clinical data.

Out of 267 patients with newly diagnosed PMR, 40 patients (15.0%) reported fever at diagnosis and we matched them according to age and sex with 80 patients without fever. The clinical characteristics of PMR_F and PMR_{NF} patients are summarised in Table I. PMR_F patients more frequently had anorexia and/or weight loss (70% *vs*. 3%; $p<0.001$) and less frequently experienced lumbar spine pain (8% *vs*. 24%; $p=0.04$). ESR was significantly higher in PMR_F patients ($p=0.004$). On PET imaging, there was no significant difference in skeletal region or large-vessel FDG uptake between both groups. Patients in the PMR_F group had a significantly longer delay prior to specialist referral ($p=0.008$) and total diagnostic delay ($p=0.004$), in addition to a relative risk of 11.5 (4.3–31.0) to be misdiagnosed with an infection. There were no differences with regard to treatment or relapse (Table I).

To our knowledge, our study is the first to determine the impact of fever at diagnosis on the clinical presentation, laboratory results, vascular FDG uptake, disease course, and treatment in patients with PMR. The PMR_F group reported significantly more anorexia and/or weight loss, which is likely provoked by systemic inflammation induced by IL6 (6, 7). This is consistent with the significantly higher ESR levels in the PMR_F group. In contrast to what we expected to find, we did not observe an increased incidence of large-vessel FDG uptake at diagnosis in the PMR_F group. This confirms earlier findings by Prieto-Peña *et al*., who reported a similar proportion of individuals with fever when comparing PMR patients with and without large-vessel FDG uptake (8). In the PMR_F group, an infectious problem was often mistakenly considered prior to specialist referral. This was associated with a significantly longer diagnostic delay and a much higher number of patients in the fever group who received a course of antibiotics prior to referral. In addition, the PMR_F group does not appear to require more intense treatment and are not at increased risk of PMR relapse during the first year.

Retrospective studies are inherently subject to variation in data integrality and confounding factors. Furthermore, fever was reported but not objectified in the majority of patients because they are often evaluated in the outpatient clinic.

In summary, fever in PMR patients is not due to an underlying large-vessel vasculitis. PMR patients with fever are at risk for diagnostic delay prior to specialist referral compared to patients without fever.

Table I. Clinical characteristics, disease course, and treatment of patients with PMR who have fever compared to those without fever.

	Fever (n=40)	No fever (n=80)	*p*-value
Demographics			
• Age at diagnosis, mean (SD), (years)	68.5 (11.1)	67.4 (10.5)	-
• Female, n (%)	20 (50)	40 (50)	-
Clinical manifestations			
• Anorexia and weight loss, n (%)	28 (70)	2 (3)	<0.001
• Morning stiffness, n (%)	22 (55)	55 (69)	0.14
• Shoulder girdle plain, n (%)	37 (93)	74 (93)	1.00
• Cervical spine pain, n (%)	5 (12.5)	20 (25)	0.15
• Lumbar spine pain, n (%)	3 (8)	19 (24)	0.044
• Hip girdle pain, n (%)	35 (88)	66 (83)	0.60
• RS3PE, n (%)	5 (12.5)	6 (8)	0.37
Laboratory results			
• CRP, mg/L, median (Q1-Q3)	69.2 (33.5-88.7)	52.4 (18-72.5)	0.09
• ESR, mm/h, median (Q1-Q3)	68.5 (44.5-89.5)	52.4 (36-66)	0.004
• Haemoglobin, g/dL, median (Q1-Q3)	12.0 (10.6-13.6)	12.7 (11.7-13.8)	0.19
PET imaging results			
• PET performed, n (%)	35 (88)	68 (85)	0.79
• Regional high FDG uptake, n (%)			
Shoulder girdle	34 (97)	66 (97)	1.00
Cervical spine	21 (60)	32 (47)	0.21
Lumbar spine	22 (63)	45 (66)	0.74
Hip girdle	32 (91)	64 (94)	0.61
Large-vessel vasculitis	4 (12)	9 (13)	0.79
Disease course			
• Delay prior to specialist consult, weeks, median (Q1-Q3)	6.5 (4-14)	4 (3-8)	0.008
• Delay after specialist consult, weeks, median (Q1-Q3)	1 (0-1)	0.6 (0-1)	0.38
• Total diagnostic delay, weeks, median, (Q1-Q3)	7.5 (4-16)	4 (3-8)	0.004
Patients with suspicion of infection prior to diagnosis, n (%)	23 (57.5)	4 (5)	<0.001
Patients who received antibiotics for presumed infection, n (%)	18 (45)	3 (3.8)	<0.001
Patients with suspicion of another musculoskeletal disorder prior to diagnosis, n (%)	8 (20)	36 (45)	0.009
• Follow up duration, months, median (Q1-Q3)	31 (19-60)	35 (15.8-60.8)	0.94
• PMR relapse (first year), n (%)	14 (35)	29 (36)	0.89
• Early PMR relapse (<3 months), n (%)	2 (5)	4 (5)	1
• Relapse as cranial GCA, n (%)	2 (5)	1 (1.3)	0.21
Treatment			
• Initial prednisone dose, mg, median (Q1-Q3)	15 (15-20)	15 (15-20)	0.73
• Maximal prednisone dose, mg, median (Q1-Q3)	15 (15-20)	20 (20-20)	0.78
• Prednisone dose escalation, n (%)	6 (15)	10 (12.5)	0.70
• csDMARD, n (%)	5 (12.5)	12 (15)	0.71

csDMARD: corticosteroid-sparing disease-modifying anti-rheumatic drug; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; GCA: giant cell arteritis; n: number; FDG,:fluorodeoxyglucose; IQR: interquartile range; PET: position emission tomography; PMR: polymyalgia rheumatica; RS3PE: remitting seronegative symmetrical synovitis with pitting oedema; SD: standard deviation.

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