Polymyalgia rheumatica patients with and without elevated baseline acute phase reactants: distinct subgroups of polymyalgia rheumatica?

D.E. Marsman[1], N. den Broeder[1], N. Boers[1], F.H.J. van den Hoogen[1,2], A.A. den Broeder[1,2], A. van der Maas[1]

[1]Department of Rheumatology, Sint Maartenskliniek, Nijmegen;
[2]Department of Rheumatology, Radboudumc, Nijmegen, the Netherlands.

Abstract

Objective

Polymyalgia rheumatica (PMR) is an inflammatory rheumatic disease characterised by pain and stiffness of neck, shoulder- and hipgirdle, typically with elevated acute phase reactants (APR). However, patients may present with normal APR. Our aim was to explore whether normal APR were due to 1) 'caught early in the disease', 2) misdiagnosis, or 3) a distinct subset of PMR with different clinical presentation and prognosis.

Methods

This was a retrospective cohort study on patients with clinical PMR diagnosis visiting the rheumatologists of the Sint Maartenskliniek from April 2008 to September 2017.

Results

Of 454 patients, 62 patients had normal, and 392 elevated APR. Normal APR patients had longer symptom duration before diagnosis (13 vs. 10 weeks; p=0.02), however, during follow-up 31% developed elevated APR. In elevated APR patients with previous APR data available while already symptomatic, 58% had earlier normal APR. Fewer normal APR patients had peripheral arthritis (2% vs. 9%;p=0.04), and anaemia (17% vs. 43%; p=0.001). More often they had a previous PMR diagnosis (16% vs. 8%; p=0.057) and a shorter median time to glucocorticoid-free remission (552 vs. 693 days; n=36 vs. 160; p=0.02). Route of GC administration differed between groups (p=0.026). Fewer patients received methotrexate; 3 vs. 12%; p=0.046). No difference in alternative diagnosis was observed.

Conclusion

PMR patients with long-term normal APR seem to be a milder subset of PMR in clinical presentation and prognosis. Additionally, our data also suggest there is a subgroup with normal APR who are caught early in the disease. Misdiagnosis does not appear to play a role.

Key words

polymyalgia rheumatica, acute phase reactants, erythrocyte sedimentation rate, C-reactive protein, disease characteristics, glucorticoid

Diane E. Marsman, MD
Nathan den Broeder, MsC
Nadine Boers, BSc
Frank H.J. van den Hoogen, MD, PhD
Alfons A. den Broeder, MD, PhD
Aatke van der Maas, MD, PhD

Please address correspondence and reprint requests to:
Diane E. Marsman,
Sint Maartenskliniek,
Department of Rheumatology,
PO Box 9011,
6500 GM Nijmegen,
the Netherlands.
E-mail: d.marsman@maartenskliniek.nl

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Introduction

Polymyalgia rheumatica (PMR) is an inflammatory rheumatic disease affecting people usually above 50 years of age (1, 2). In this age group, the highest incidence is seen in Northern Europe, varying from 41 to 113 per 100.000 persons (1). The cause is unknown and the diagnosis is made on clinical presentation and laboratory testing. Typical symptoms are bilateral pain and stiffness of the neck, shoulder- and hip girdle, with elevated inflammatory parameters (1, 2). However, there is no golden standard to diagnose PMR and it can be challenging due to its heterogeneous and frequently atypical presentation, especially when patients have normal acute phase reactants (APR) at diagnosis (2).

A high erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP) are important markers for diagnosis and assessment of PMR activity, with considerable negative predictive value for the diagnosis (2). PMR without increased APR at presentation however does exist. The proportion of patients with clinical diagnosis of PMR and normal APR at baseline was examined in a few observational studies with various quality of evidence and is reported in 1.1 to 22.5% of PMR patients (3, 4). These studies mostly examined ESR and less frequently CRP.

We hypothesise three different possible reasons for the lack of increase of APR in a patient with PMR. Firstly, patients with normal APR at diagnosis might have the same pathophysiology and characteristics as patients with elevated APR, but just caught earlier in the disease course, with an increased APR at a later stage.

A second possibility would be that patients with normal APR are a distinct pathophysiological subgroup of PMR patients with different disease causality and treatment outcomes, representing a milder clinical phenotype, with possibly also a more benign and less refractory course. Indeed, findings of baseline differences reported in previous studies support this hypothesis, as patients with normal APR at baseline were younger, had less systemic signs (4, 5), a higher mean haemoglobin value (2, 5-8), and also had significantly longer duration of symptoms prior to diagnosis (9). However, there is inconsistency since other studies found no differences in clinical characteristics and disease course in patients with normal and elevated APR (2, 4, 7, 10). Additionally, comments can be made on quality of evidence, with some studies carried out in very few patients (7), and/or inclusion of patients with concomitant giant cell arteritis (GCA) (4, 7, 10).

To corroborate the theory of different pathophysiological subgroups it can be hypothesised that there are different disease spectra. Some immunological differences have already been described in patients with PMR *versus* GCA, maybe this is also the case with normal *versus* elevated APR patients. Amongst others, differences in localised temporal artery cytokine patterns and serum markers related to immune cells was described in PMR and GCA patients (11, 12). With regard to differences between normal and elevated APR marked depletion of CD8+ cells in peripheral blood of PMR patients with low ESR has been described, compared to higher levels in PMR patients with high ESR values, and even higher levels in normal controls (13). In conclusion, there are indications of pathophysiological differences between different disease spectra in PMR.

A third option is that patients are incorrectly diagnosed with PMR and have another diseases (such as, amongst other, rheumatoid arthritis, osteoarthritis, shoulder bursitis or enthesopathy). Although most cohorts and case series use course after prolonged follow-up as reference standard for the diagnosis to prevent this (2, 7), there is no golden standard to diagnose PMR or a PMR flare.

In conclusion, evidence remains scarce and it is still unclear whether PMR patients with normal baseline APR are the same as PMR patients with elevated baseline APR but earlier diagnosed in their disease course, whether they represent a distinct subgroup of PMR, or whether they are misdiagnosed patients. We therefore aim to compare baseline and treated follow-up characteristics between patients with normal and increased APR at diagnosis.

Methods

Study design

This is a retrospective explorative cohort study of newly diagnosed PMR patients, who visited the outpatient rheumatology clinic of the Sint Maartenskliniek over a ten-year period from April 2008 to January 2018. Diagnosis, treatment and follow-up were made according to local protocol, which follows the EULAR/ACR 2015 recommendations on PMR management (3).

Patients

Inclusion criteria: All patients with a new clinical diagnosis of PMR or a new episode of PMR who had a follow-up of at least 9 months (minimum duration of GC-treatment) were eligible for inclusion. The date for inclusion in the cohort was the date of diagnosis by the treating rheumatologist, or by the general practitioner, if later confirmed by the rheumatologist. The diagnosis of PMR was made as judged clinically by the treating rheumatologist, and no formal classification criteria were used as inclusion criteria.

Exclusion criteria: We excluded patients who at baseline had a current and active GCA, rheumatoid arthritis, treatment with disease-modifying antirheumatic drugs (DMARDs) regardless of indication, if there was uncertainty about the PMR diagnosis as described by the treating physician, or treatment with glucocorticoids (GC) more than four weeks prior to inclusion date (irrespective of reason for prescribing). The justification of not including patients treated with GC for more than four weeks prior to inclusion date was to enhance the quality of the collected data and ensure that collection of ESR and CRP was as complete as possible. Patients were not included if the PMR diagnosis changed within the first 9 months of follow-up.

Assessments

Data was collected from the referral letter from the general practitioner (GP) and the electronic health record. All data of visits were collected, until censoring of follow-up (January 1 2018), or until patients were either lost to follow-up or deceased. At baseline (either from the GP referral letter or electronic health record) we collected data on previous medical history, clinical symptoms and duration, physical examination, laboratory and additional imaging research, as obtained by the treating physician according to local protocol. We collected the course of the disease (signs and symptoms, CRP/ESR), and treatment, including route of and the GC starting dose in mg at baseline and the GC dose in mg at every follow-up visit, and thereby every dosage decrease and increase respectively, and the use of concomitant DMARDs. Baseline APR were collected prior to start of GC.

Laboratory analysis

ESR was determined by the 30 minute automated version of the Westergen method. This method measures the ESR after 30 minutes and extrapolates it to 60 minutes through a specific algorithm, and has excellent agreement with manual 1 hour Westergren (14). In our study a value above 30mm/hour was considered elevated for both men and women. High sensitivity CRP was determined by the chemical analyzer Olympus type AU400 (Goffin Meyvis), with an upper limit of normal of 10 mg/L (1mg/dl).

Sample size calculation

Due to the explorative nature of the study, no formal sample size calculation was made. To calculate the precision that can be reached concerning the primary endpoint, we assumed a proportion of APR negative patients to be 10%, in light of previous studies reporting normal BSE and/or CRP in 1.1–22% of PMR patients (6,7). Calculation of the confidence interval around a proportion of 10% normal APR with $p+/-1.96\sqrt{(p(p(1-p))/n)}$ shows that precision of –3% and + 3% can be reached with a sample size of 384 patients.

Statistical analysis

Descriptive statistics were used [using mean (SD), median (p25-p75) or n (%) as appropriate], and differences between patients with normal *versus* high APR (CRP >10 mg/L and/or ESR >30mm/hour) were tested using Fisher's exact test for categorical data, *t*-test for normally and Wilcoxon test for non-normally distributed data. All analyses were performed with STATA/IC v. 13.1.

Ethical declaration

We obtained permission from the medical ethics committee of research with human subjects (CMO region Arnhem-Nijmegen, 2017-3506), and it was decided that our study does not fall under the scope of the Medical Research Involving Human Subjects Act (WMO). The local research approval committee approved this study (RR-168-PMR). Consent was obtained using an opt out letter procedure, according to Dutch law (WGBO 458.2c). If patients objected to the use of their data for this study, their data was not collected.

Results

A total of 880 PMR patients visited the Sint Maartenskliniek between April 2008 to January 2018. Of these 880 patients, 454 (52%) were included. Reasons for exclusion were insufficient baseline data (3%), refractory PMR/second opinion (16%), insufficient follow-up (3%), not fulfilling the inclusion criteria (20%), objection to participating in the study (1%), not able to collect opt-out due to death (4%) and migration (1%). Baseline characteristics of patients with normal *versus* elevated APR are described in Table I and follow-up characteristics in Table II. Sixty-two (14%) patients had normal, and 392 (86%) had elevated APR. Patients with normal APR had a longer median duration of symptoms before diagnosis (13 *vs*. 10 weeks; p=0.02). Also they were more likely to have a previous diagnosis of PMR (16 *vs*. 8%; p=0.06).

Fewer patients with normal APR had peripheral arthritis (2 *vs*. 9%; p=0.04) and anaemia at diagnosis (17 *vs*. 43%; p=0.001). However, no differences were found in distal swelling or pitting o edema, systemic symptoms, the presence of rheumatoid factor (RF) or anti-citrullinated C-peptide (ACPA), osteoarthritis, cardiovascular disease or diabetes.

Of the 392 patients with baseline elevated APR, we were able to collect APR previous to PMR diagnosis in 191 patients, during the period in which

Table I. Baseline characteristics of patients with normal *versus* elevated APR.

Characteristic	Normal APR (n=62; 14%)	Elevated APR (n=392; 86%)	*p*-value
Patient characteristics			
Female (%)	32 (52)	218 (56)	0.238
Age in years at diagnosis (SD)	66.0 (7.5)	66.6 (8.9)	0.594
History of previous PMR (%)	10 (16)	32 (8)	0.057
Disease characteristics			
Weeks with PMR symptoms before diagnosis (IQR)*	**13 (7-20)**	**10 (6-16)**	**0.020**
Neckpain (%)	27 (44)	175 (45)	0.388
Bilateral shoulder pain /stiffness (%)	57 (93)	361 (92)	1.000
Bilateral hip pain/stiffness (%)	55 (87)	327 (83)	0.352
Both bilateral shoulder- and hip pain/stiffness (%)	52 (84)	310 (79)	0.496
Peripheral arthritis (%)*	**1 (2)**	**35 (9)**	**0.044**
Distal swelling and pitting oedema (%)	1 (2)s	11 (3)	1.000
Systemic symptoms** (%)	27 (44)	172 (44)	1.000
ESR in mm/hour (IQR)	19 (12-25)	42 (31-53)	
CRP in mg/l (IQR)***	5 (2-7)	34 (21-57)	
Anaemia (%)*	**8 (17)**	**132 (43)**	**0.001**
Morning stiffness >45 min (%)	29 (73)	206 (68)	0.197
Rheumatoid factor present**** (%)	4 (11)	34 (13)	1.000
Anti-CCP present**** (%)	0 (0)	3 (1)	1.000
Comorbidities			
Osteoarthritis (%)	22 (35)	163 (42)	0.406
Hypercholesterolaemia (%)	10 (16)	86 (22)	0.402
Diabetes mellitus (%)	4 (6)	52 (13)	0.149
Hypertension (%)	25 (40)	145 (37)	0.672
Thyroid disease (%)	2 (3)	38 (10)	0.136
Ischaemic heart disease ‡ (%)	5 (8)	40 (10)	0.819
Other cardiovascular disease‡‡ (%)	4 (6)	39 (10)	0.407
Initial treatment			
GC treatment*			
Oral GC only (%)	**38 (61)**	**281 (72)**	**0.026**
Oral GC + MP i.m. 120 mg (%)	**20 (32)**	**105 (27)**	
MP i.m. only* (%)	**4 (6)**	**6 (2)**	
Starting dose oral GC in mg (IQR) ‡‡‡	15 (15-20)	15 (15-20)	0.595

*Significant with appropriate test; **Fever, night sweats, weight loss, anorexia; ***n=46 in normal APR group; n=358 in elevated APR group; ****Rheumatoid factor: n=36 *vs*. n=257; anti-CCP: n=33 *vs*. n=242; ‡Angina pectoris, myocardial infarction; ‡‡Cardiovascular disease: cerebrovascular event, peripheral arterial disease, heart failure, thrombosis; ‡‡‡ n=42 in normal APR group; n=339 in elevated APR group.

PMR symptoms already existed, with (up to one year prior to diagnosis). Of these patients, 110 (58%) had no previous elevated APR while having PMR symptoms, and 81 (42%) had previous elevated APR. The median duration of PMR symptoms in these patients was 12 weeks (6–17) and 9 weeks (7–16; p=0.43), respectively. The route of GC administration differed between the groups (oral GC only 61 *vs*. 72%, both oral and intramuscular GC 32 *vs*. 27%, intramuscular GC only 6 *vs*. 2%; p=0.026). After GC initiation, 31% of the patients with normal APR developed elevated APR later during the disease course compared to 59% in the elevated APR group (p=0.0001).

There was no difference of route of GC administration and starting oral GC dose (15mg; IQR 15–20mg) between groups. Additionally, no differences in response to GC after 4 weeks, time to first flare and total number of flares per patient were found between groups. In both groups, however, the total number of flares was higher in the second year of follow-up compared to the first year (34 *vs*. 13%; and 30 *vs*. 20%; p=0.001 in the normal and elevated APR group respectively). In the normal APR group, fewer patients used methotrexate (3 *vs*. 12%; p=0.046). During follow-up, no differences were found in the proportion of patients with an additional new diagnosis of GCA, RA or malignancy. Patients with normal APR at diagnosis were more often referred back to the general practitioner (n=58 *vs*. 4%; p=0.003) and thereby earlier (85 *vs*. 109 weeks; IQR 61–108 and 73–142, respectively).

Discussion

A first conclusion of this study is the finding that a considerable proportion of patients with a clinical PMR diagnosis can indeed present with normal APR at diagnosis. Regarding our hypotheses whether this lack of elevated APR in PMR patients is due to the fact that they a) were caught early in the disease, b) are a distinct subgroup or c) are incorrectly diagnosed with PMR, we found most evidence for b), some indication for a), but no support for c).

Starting with the hypothesis that patients with normal APR are caught earlier in disease, we found that patients with normal APR had a longer median duration of PMR symptoms prior to diagnosis, even though the frequency of PMR symptoms like neck-, shoulder- and hip girdle symptoms were the same in both normal and elevated APR patients. This time effect in elevation of APR has been studied in two previous small studies. One study reported delayed elevation of ESR/CRP during follow-up and after start of GC treatment in 2 out of 26 patients (6). In another case series of 10 patients with ESR <35 mm/h who were treated with GC, no delayed elevation of ESR was observed during follow-up (7).

Our finding does not support the hypothesis that these PMR patients who are caught earlier in their disease course are therefore APR negative, but rather suggests a delay in diagnosis possibly due to the atypical presentation with normal APR symptoms. This notion is also supported when we looked at prior CRP and ESR values before diagnosis was made in patients with elevated APR at diagnosis, because patients who had prior normal values of CRP and ESR and baseline elevated APR had a longer duration of PMR symptoms than patients who had elevated APR at baseline and prior elevated APR. However, these patients had still presented themselves to the physician with symptoms

Table II. Follow-up (FU) characteristics of patients with normal *versus* elevated APR.

Characteristic	Normal APR (n=62; 14%)	Elevated APR (n=392; 86%)	*p*-value
Insufficient response to GC at 4 weeks (%)***	16 (26)	83 (21)	0.411
Patients who developed elevated APR during FU (%)	19 (31)	231 (59)	0.0001
Median time in weeks to first flare in flare patients (IQR)	41 (19-68)	39 (23-64)	0.964
Total patients with flares during FU (%)	36 (58)	259 (66)	0.271
1 flare (%)	15 (24)	124 (32)	0.387
2 flares (%)	7 (11)	61 (16)	
3 or more flares (%)	14 (23)	69 (18)	
Patients with flares during FU*			
Total (%)	36 (58)	254 (65)	0.321
<12 months (%)	8 (13)	77 (20)	0.289
12-24 months‡ (%)	21 (35)	114 (30)	0.553
DMARD ‡‡			
Methotrexate (%)*	**2 (3)**	**48 (12)**	**0.046**
Azathioprine (%)	0	8 (2)	0.606
Leflunomide (%)	0	3 (1)	1.000
TCZ (%)	0	1 (0)	1.000
Other (%) ‡‡‡	0	8 (2)	0.606
Rheumatoid arthritis (%)	2 (3)	21 (5)	0.755
Giant cell arteritis (%)	1 (2)	7 (2)	1.000
Malignancy**** (%)	0	13 (3)	0.230
Death (%)	0	1 (0)	1.000
Time in weeks to referral GP in GC-free remission (IQR)*	**85 (61-108)**	**109 (73-142)**	**0.003**
Proportion of GC-free remissio**			
12 m FU (%)	14 (23)	111 (29)	0.444
24 m FU (%)	25 (52)	136 (44)	0.395

*Significant with appropriate tests at alpha level 0.05; **Normal APR at 12 months n=61 and at 24 months n=48, elevated APR n=380; and at 24 months n=309; ***Remission defined by rheumatologist (clinical judgement); ****Types of malignancy: bladder cancer (2), renal cell carcinoma, ovarian cancer, Grawitz tumour, leukaemia, skin tumour, squamous cell carcinoma, choleduchus carcinoma; ‡Total patients who flared at 12–24 months was significantly higher than total patients who flared before 12 months, in both normal and elevated APR group; ‡‡Reason for prescribing disease-modifying drugs (DMARD) in elevated APR: ineffectiveness GC: methotrexate (MTX) 23, azathioprine (AZA) 6; tocilizumab (TCZ) 1; adverse events GC: MTX 4, ineffectiveness and adverse events GC: MTX 7, AZA 3, other disease: MTX 4; ‡‡‡ Hydroxochloroquine, sulfasalazine, etanercept and adalimumab were prescribed in 8 patients due to other diseases than PMR.

while APR were normal, so this could also mean that they could have been "caught early" but the diagnosis was not made because of the normal APR. Additionally, the fact that some patients with normal APR at diagnosis were able to develop elevated APR after GC initiation Later, during the disease course, also suggests that they may have been "caught early".

We found most evidence for the second hypothesis that patients with normal APR represent regular PMR, albeit in a milder clinical phenotype. At baseline fewer cases have peripheral arthritis and anaemia at diagnosis, but no other differences were observed. A possible hypothesis could be that in patients with more signs of inflammation, for example in patients with additional peripheral arthritis, higher interleukin-6 levels stimulate the production of ESR and CRP. Our results match previous studies that found milder disease presentation at diagnosis (5, 8, 15). However, not all studies found these differences (4, 6). And unlike some earlier studies we did not find a differences between systemic signs (4-6, 8), gender (6, 8) or age (4).

These contrasts could partly be explained by the smaller sample size in earlier studies. In addition, discrepancies could be explained by the design of the study and selection bias. Some studies used different inclusion criteria, and included patients who had both PMR and GCA, possibly representing a more severe subset of PMR. Our study is conducted with a larger sample size with solely PMR patients, therefore our results may be more precise and less biased.

Evidence for this second hypothesis is also shown by the fact that during follow-up patients with normal APR had a better prognosis as more patients were referred back earlier to the GP in GC-free remission. Furthermore, disease-modifying anti-rheumatic drugs were prescribed less often in normal APR patients. This finding in line with other studies that found patients with normal ESR/CRP had a shorter treatment duration and higher proportion of patients able to discontinue GC (5,9,15). One previous study found no differences in proportion and time to remission (8). We found no difference in flares and relapses, which is consistent with some studies (4, 8, 16, 17), but not all (4,16-18). No previous study examining differences in patients with *versus* without normal APR, reported the use of DMARDS in PMR patients.

The results from our study do not support the third hypothesis that patients with normal APR at diagnosis are misclassified as having PMR. Firstly, many patients (31%) develop increased APR when flaring later on in disease course. Also, RA is not more frequently diagnosed during follow-up. However, the nature of our retrospective cohort was such that it was not possible to evaluate other alternative diagnosis such as osteoarthritis. We included patients with a "definitive" PMR, as judged by the treating clinical physician with confirmation also during follow-up, and if a patients' diagnosis was changed to for example osteoarthritis, this patients would not be included. One other study also reported no alternative diagnoses during follow-up (7).

Strengths of this study are the large sample size, long follow-up, and the fact that we included patients with only clinical PMR and no clinically suspect GCA. Limitations include the retrospective character, introducing possible biases due to missing data. Because of the retrospective character, we could not assess the severity of the different disease activity domains like stiffness or functioning. It could be interesting to see whether these are different in normal *versus* elevated APR. Another possible limitation of this study is index event bias. For example patients with baseline elevated APR who had previous normal APR while having

PMR symptoms, were not recognised as having PMR at that moment, and it is debatable whether the date the patients first went to the doctor with PMR symptoms should have been the index event instead of the date of diagnosis. Furthermore, more patients with normal APR had a previous history of PMR. Unfortunately, it is unknown whether the APR were elevated during the first episode of PMR. Possibly the diagnosis was made easier in these patients due to their previous history and recognition of their symptoms. The generalisability also has its limitations, as the findings of this cohort may not be representative of all PMR patients, for example patients treated in the first line. Furthermore, most PMR patients are treated in the first line and only referred to an outpatient rheumatology clinic when there is good reason for doing so, such as uncertainty about the diagnosis (for example normal APR) or a difficult to treat PMR. This limits the generalisability of this PMR cohort to all PMR patients as this is only a referred subset. It may be that the occurrence of normal APR in a referred subset of PMR patients is higher compared to PMR patients treated in the first line only. Moreover, all referred PMR patients in general could have a more severe and difficult to treat PMR compared to first line patients. Little is known about first line PMR patients and it would be interesting to compare first and second line PMR patients in terms of clinical presentation and prognosis. Furthermore, interestingly only 2% of our PMR patients developed GCA during follow-up. This is far less than the usual reported GCA incidence of 16–20%. Future research on the epidemiology of PMR, GCA and concurrence of these diseases could provide answers as to whether the incidence in the Netherlands is indeed lower than in countries with a different genetic make-up and environmental factors.

In conclusion, this study confirms findings from earlier studies that PMR can indeed present with normal APR and that – even though diagnosing PMR with normal APR remains a challenge, as shown with delayed diagnosis and the lack of a golden standard diagnostic test – clinicians can indeed diagnose PMR when APR are normal. Furthermore, this study confirms with a larger sample size of solely PMR patients that patients with normal APR are indeed a distinct subset with milder disease presentation and prognosis, with possibly a different pathophysiological pathway in the same spectrum of disease.

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Key messages

- Around 15% of polymyalgia rheumatic (PMR) patients have normal acute phase reactants (APR)
- PMR patients with normal APR seem a milder subset of PMR in clinical presentation and prognosis
- Misdiagnosis of PMR instead of rheumatoid arthritis does not appear to play a role.

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