Seasonal onset of polymyalgia rheumatica: correlations with the pattern of clinical presentation, disease severity and outcome in 383 patients from a single centre

A. Sobrero[1], S. Paolino[1], E. Hysa[1], D. Camellino[2], V. Tomatis[1], M. Cutolo[1], M.A. Cimmino[1]

[1]Research Laboratory and Academic Division of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Italy;
[2]Division of Rheumatology, La Colletta Hospital, Azienda Sanitaria Locale 3, Arenzano, Italy.

Abstract

Objective

Polymyalgia rheumatica (PMR) is an inflammatory disorder, more common in the elderly, characterised by girdle pain and stiffness, constitutional symptoms and raised serological markers of inflammation. Studies on the seasonality of onset of PMR have shown conflicting results, possibly due to the different diagnostic criteria and onset recognition. In this study, the month of onset of PMR was evaluated in patients originating from one geographical area, visited by the same clinician.

Methods

In 383 PMR patients (245 women, median age 73 years, range 47–92 years) examined between 1990 and 2014, PMR was diagnosed according to Bird's criteria. The month of onset was recorded systematically during the patient's interview. Clinical features initially recorded included the location of joint involvement, the coexistence of temporal arteritis (TA) or peripheral arthritis, and the type of onset (acute if reported of 72h or less). Patient follow-up, PMR severity and outcome were also recorded throughout the study.

Results

We failed to identify any peak month (p=0.93) or season (p=0.45) for the onset of PMR. Timing of onset did not correlate with the clinical features, severity or outcome of PMR. Only when patients were also affected by concomitant TA, the onset of PMR was more often seen in Autumn (p=0.02). Patients with PMR onset in Autumn also has a greater risk of developing TA during their follow-up (p=0.03). By multiple regression, the only outcome predicted by Autumn onset was use of methotrexate (p=0.039).

Conclusion

PMR showed no seasonality of onset, except for the subset associated with TA. A risk factor with seasonal variation is suggested for the pathogenesis of this form of PMR.

Key words
polymyalgia rheumatica, temporal arteritis, giant cell arteritis, month of onset, seasonality

*Alessia Sobrero, MD**
*Sabrina Paolino, MD, Assist. Prof.**
Elvis Hysa, MD
Dario Camellino, MD, PhD
Veronica Tomatis, MD
Maurizio Cutolo, MD, Prof.
Marco A. Cimmino, MD, Prof.

**These authors share first authorship.*

Please address correspondence to:
Marco A. Cimmino,
Clinica Reumatologica, DIMI,
Università di Genova,
Viale Benedetto XV, 6,
16132 Genova, Italy.
E-mail: cimmino@unige.it

Received on April 4, 2020; accepted in revised form on May 25, 2020.

Competing interests: none declared.

Introduction

Polymyalgia rheumatica (PMR) is an inflammatory disorder most often seen in the elderly characterised by girdle pain and stiffness, constitutional symptoms and raised serological markers of inflammation, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). The aetiology of PMR is still unknown, but both genetic and environmental factors possibly linked with a seasonal distribution, may be involved (1). The sudden onset of PMR and its different incidences rates, higher in the Scandinavian countries and lower in the Mediterranean, Middle-Eastern and Asian countries, suggest the view that an external trigger is at play (2). This could be an infection, such as those caused by *Mycoplasma pneumoniae* (3), *Parvovirus B19* (4), and *Parainfluenza virus* (5). Another consideration that could point to seasonality of disease onset is damage of the superficial arteries, such as the temporal artery, related to ultraviolet radiation exposure (UV). On occasion, exposure of the vessel wall internal elastic lamina to UV light can induce granulomatous inflammation, which is histologically similar to that of giant cell arteritis (GCA) (6). By disrupting the tunica adventitia, inflammation could elicit new antigens formation with ensuing endothelial damage (7).

We have previously shown that PMR has a more frequent onset in the warmer months in Northern Italy (8). A seasonality, even though not always in the warmer months, has been confirmed in several studies, but not in others (9). These conflicting results are possibly due to differences in the criteria of diagnosis and onset recognition of PMR. A large, epidemiologically sound study, performed in the same geographical location and with the same method is deserved in order to confirm onset seasonality. In the this work, the seasonality of onset of PMR has been investigated in patients from the Liguria Region of Italy examined by the same clinician over 24 years. The season of onset of PMR was correlated with the patient's clinical features and laboratory investigation. In addition, the role of the season of onset in predicting PMR outcome was also evaluated.

Patients and methods

Consecutive patients referred to two outpatient clinics (from a tertiary rheumatology centre and a private practice) for the suspicion of PMR between February 1990 and September 2014 were asked to specify the month of onset of their disease. PMR onset was defined as the appearance of the first symptom that was later related to PMR. A total of 477 patients, diagnosed according to Bird et al. criteria (10), were screened. Of them, 94 were not included in the study because i) they could not remember the month of onset; ii) initial clinical information was missing because they had been seen at first visit in another institution; iii) a different final diagnosis was formulated during follow-up; or iv) because they denied permission to use their data. The excluded patients were similar to those included in terms of gender [63 (67%) women and 31 (33%) men] and age (median 71 years, range 51–104 years). In fact, of the 383 patients included in the study, 245 (64%) were women, and median age was 73 years (range 47–92 years).

Standardised questionnaire and examination forms were used. Clinical features recorded at disease presentation included initial involvement of: i) the shoulder girdle; ii) the pelvic girdle; iii) the vertebral column; iv) two or more of the previous locations; v) temporal arteritis (TA); vi) acute onset, *i.e.* reaching the full expression of PMR in less than 72h; or vii) peripheral arthritis. TA was diagnosed when the ACR classification criteria for giant cell arteritis (GCA) (11) were fulfilled. We used the term TA, not GCA, because only the cranial form of vasculitis was considered.

Disease severity was evaluated by considering: i) weight loss; ii) fever; iii) morning stiffness; iv) ESR; v) CRP; and vi) initial dose of prednisone or prednisone equivalent (PDN).

PMR outcome was evaluated in terms of the following: i) cumulative dosage of PDN; ii) number of relapses, defined as occurrence of PMR or TA symptoms and elevation of CRP and/or ESR during GC tapering or after its discontinuation; iii) use of methotrexate (MTX); iv) remission at the last follow-up visit;

v) being on PDN at the last follow-up visit and its dosage; vi) occurrence of TA during follow-up; vii) occurrence of peripheral arthritis during follow-up; and viii) death.

The institutional review board granted permission to review the clinical data. At first visit, the patients received a leaflet describing the characteristics of their disease and explaining that their clinical history and findings would have been used for research purposes, if they granted their verbal permission.

The month of onset of PMR was investigated with a specific question asked by the same researcher, who tried to facilitate the patients' memory by connecting this date with other relevant personal events or public news. This information was obtained for 383/477 (80.3%) patients. The months of onset were arbitrarily aggregated in seasons, with Summer including the months July-September, Autumn in October-December, Winter in January-March, and Spring in April-June. This was necessary because it was impossible in most cases to evaluate the very day of onset and to adjudicate it to the traditional astronomic season.

Statistical analysis

Means were compared by the Student's t-test or by one way analysis of variance if their distribution was normal and by the Kruskall Wallis test when it was non-parametrical. Frequencies were compared by the chi square test. Correlations were analysed through the Spearman's rho test. Multiple regression was calculated including seasons of onset as dependent variables and the PMR outcomes showing a $p<0.3$ in univariate analysis as independent ones. *p*-values less than 0.05 were considered significant. All the calculations were performed using Medcalc® v. 19.2.1 (Belgium) as statistical software.

Table I. Demographic data, clinical and laboratory results in our PMR cohort.

Sex (F/M)	245/138
Age at PMR onset (years)	73 (47-92)
Weight (kg)	70 (40-107)
Height (cm)	165,7 ± 8.9
BMI	25.7 (17.7-41.4)
Weight loss (yes/no)	111/265 (29.5%)
Fever (yes/no)	86/291 (22.8%)
Morning stiffness (minutes)	60 (0-720)
Onset with shoulder girdle involvement (yes/no)	332/48 (87.4%)
Onset with hip girdle involvement (yes/no)	253/123 (67.3%)
Simultaneous onset of both girdles (yes/no)	184/192 (48.9%)
Onset with spine involvement (yes/no)	149/227 (39.6%)
Onset with temporal arteritis (yes/no)	28/348 (7.4%)
Acute onset (yes/no)	80/295 (21.3%)
Interval between PMR onset and GC initiation (months)	2 (0-90)
Initial GC dose (mg)	12.5 (0-50)
Erythrocyte sedimentation rate (mm/h)	54 (1-122)
C-reactive protein (mg/dl)	29 (1-239)
Platelet count (x10^3/mL)	317.5 (129-723)
Season of onset (Summer/Autumn/Winter/Spring)	104/85/96/92
Duration of follow-up (days)	459 (0-7500)
Peripheral arthritis at onset (yes/no)	77/298 (20.5%)
Peripheral arthritis at follow-up (yes/no)	60/313 (16.1%)
Temporal arteritis at follow-up (yes/no)	17/358 (4.5%)
Cumulative PDN dosage (mg)	2038 (0-26175)
Number of relapses	0 (0-10)
Use of methotrexate (yes/no)	99/277 (26.3%)
Remission at last visit (yes/no)	292/82 (78.1%)
On GC at last visit (yes/no)	204/168 (54.8%)
PDN dose at last visit (mg)	1.9 ± .3
Death (yes/no)	44/323 (12%)

BMI: body mass index; GC: glucocorticoid; PDN: prednisone.

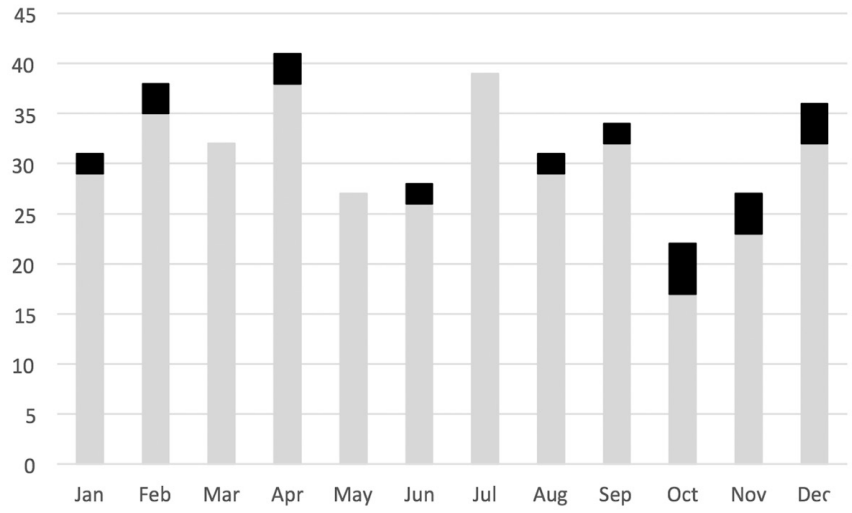

Fig. 1. The columns show the number of polymyalgia rheumatica patients divided according to the month of onset; the black area corresponds to the subgroup with concomitant temporal arteritis at onset.

Results

The demographic, clinical and laboratory characteristics of PMR patients are shown in Table I. Their median follow-up was 459 days (range 0–7500 days). April was the month in which symptoms more frequently started (41 patients or 10.7%), whereas October was the month with the lowest frequency of PMR onset (22 patients or 5.7%) (Fig. 1). There was no difference in the frequency of PMR onset between months (p=0.93) or between seasons (p=0.45). Twenty-eight (7.3%) patients had simultaneous onset of PMR and TA. During follow-up, 17 (4.4%) patients showed TA; of them, 8 already had it at PMR onset, experiencing a recurrence, whereas 9 had new-onset TA.

Concomitant TA at PMR onset was more frequent when PMR initiated in Autumn (p=0.02) (Fig. 1). Patients with PMR onset in Autumn also had a greater risk of developing TA during

Table II. Comparison of demographic data, and clinical and laboratory results according to the season of onset of PMR.

Characteristic	Summer n=104	Fall n=85	Winter n=98	Spring n=96	*p*
Sex (F)	71 (68.3)	56 (65.9)	62 (63.3)	56 (58.3)	0.51
Age at PMR onset (years)	72 ± 8.9	71.3 ± 8.6	73.3 ± 8.1	72.6 ± 8.8	0.43
Weight (kg)	71.7 ± 13.2	69.2 ± 12.0	70.5 ± 12.5	69.7 ± 11.0	0.62
Height (cm)	166.3 ± 9.1	165.8 ± 9.9	164.8 ± 8.6	165.6 ± 8.0	0.86
BMI	26.3 ± 3.4	25.5 ± 3.3	26.1 ± 4.1	25.1 ± 3.1	0.29
Weight loss (%)	28 (26.9)	30 (35.3)	27 (27.6)	27 (28.1)	0.62
Fever (%)	23 (22.1)	14 (16.5)	25 (25.5)	24 (25)	0.40
MS (minutes)	60 (0-720)	60 (0-360)	60 (0-480)	60 (0-500)	0.67
Onset with shoulder girdle involvement (%)	89 (85.6)	74 (87.1)	86 (87.8)	86 (89.6)	0.86
Onset with hip girdle involvement (%)	71 (68.3)	58 (68.2)	61 (62.2)	65 (67.7)	0.77
Simultaneous onset of both girdles (%)	49 (47.1)	42 (49.4)	43 (43.9)	52 (54.2)	0.54
Onset with spine involvement (%)	43 (41.3)	36 (42.4)	36 (36.7)	38 (39.6)	0.87
Onset with temporal arteritis (%)	4 (3.8)	13 (15.3)	5 (5.1)	6 (6.3)	0.02
Acute onset (%)	21 (20.2)	20 (23.5)	21 (21.4)	19 (19.8)	0.92
Interval PMR onset and GC start (months)	2 (0-13)	2 (0-90)	1.5 (0-17)	2 (0-18)	0.39
Initial GC dose (mg)	12.5 (0-37.8)	15 (0-37.5)	12.5 (0-50)	12.5 (0-50)	0.25
ESR (mm/h)	55.3 ± 28.5	55.8 ± 26.2	59.7 ± 30.3	56.4 ± 30.6	0.75
C-reactive protein (mg/dl)	34.5 41.3	41.5 40.1	0.47		
Platelet count (x10^3/mL)	346 (165-672)	319 (195-572)	316 (129-723)	316 (135-690)	0.57
Duration of follow-up (days)	486 (14-4141)	455 (0-5580)	533 (0-4207)	400 (0-7500)	0.78
Peripheral arthritis at onset (%)	21 (20.2)	14 (16.5)	23 (23.5)	20 (20.8)	0.69
Peripheral arthritis at follow-up (%)	16 (15.4)	11 (12.9)	21 (21.4)	12 (12.5)	0.27
Temporal arteritis at follow-up (%)	1 (1)	8 (9.4)	3 (3.1)	5 (5.2)	0.03
Cumulative GC dosage (g)	2.1 (0-20.8)	2.5 (0.2-26.2)	2.0 (0-20.8)	1.6 (0-12.8)	0.21
Number of relapses	0 (0-6)	1 (0-6)	0 (0-5)	0 (0-10)	0.77
Use of methotrexate (%)	31 (29.8)	28 (32.9)	25 (25.5)	16 (16.7)	0.07
Remission at last visit (%)	86 (82.7)	66 (77.6)	74 (75.5)	68 (70.8)	0.26
On GC at last visit (%)	52	50	55	49	0.52
GC dose at last visit (mg)	1.25 (0-25)	2.5 (0-25)	2.5 (0-25)	1.25 (0-25)	0.59
Death (%)	14 (13.5)	8 (9.4)	14 (14.3)	9 (9.4)	0.57

BMI: body mass index; GC: glucocorticoid; PDN: prednisone.

Table III. Regression equation and analysis of variance of the least squares multiple regression including seasons of onset as dependent variables and the PMR outcomes showing a $p<0.3$ in univariate analysis as independent ones.

Independent variables	Coefficient	Std. Error	t	*p*-value	rpartial	rsemipartial
(Constant)	2.7273					
Cumulative GC dosage	-0.000007186	0.00001810	-0.397	0.6916	-0.02089	0.02062
Temporal arteritis at follow-up	0.3946	0.3047	1.295	0.1960	0.06802	0.06730
Use of methotrexate	-0.3108	0.1502	-2.069	0.0392	-0.1083	0.1075
Remission at last visit	-0.2181	0.1455	-1.498	0.1350	-0.07861	0.07784
Peripheral arthritis at follow-up	0.05214	0.1658	0.314	0.7534	0.01654	0.01633

Source	Degrees of freedom	Sum of squares	Mean square
Regression	5	12.1640	2.4328
Residual	361	463.3401	1.2835
F-ratio	1.8955		
Significance level	p=0.0944		

their follow-up (p=0.03). However, if only patients with new-onset TA during follow-up were considered, this difference was not significant (p=0.59). Except for TA, the season of onset was not associated with PMR severity or the patient's clinical features (Table II). There were no significant correlations between month of onset and continuous variables (data not shown). By multiple regression, the only outcome predicted by the peak of Autumn onset was use of MTX (p=0.039) (Table III).

Discussion

There was no seasonality of PMR onset in this study on a large cohort of PMR patients from the same geographical area examined by the same clinician. This result is different from that observed in the past in three locations of Northern Italy, including Liguria (8). In this study from our group, a higher rate of PMR onset in the warmer months was reported. Several papers have been published on the seasonality of onset of PMR and GCA, with contrasting results. In a recent meta-analysis (9), of the 22 evaluated papers, the majority (15 or 68.2%) showed a seasonality of onset. This occurred in the warm months in eight studies. Even if most of these studies come from a limited number of countries (UK, France, Italy, and Norway), there is no indication that the geographical location of the study population affects the seasonality pattern.

These studies are biased by heterogeneity, which hurdles comparison. In particular, different diagnostic criteria

were used, and the method to determine the month of onset was not homogenous. Most authors relied on the starting time of symptoms reported by patients, others on the date of the first clinical examination, and some on a variety of methods. Therefore, a suitable large study from a given area, with strict and consistent criteria of patient enrolment and definition of month of onset, was worth performing, although its results cannot be generalised. After the completion of our previous study in 1990, we decided to continue to investigate a larger group of PMR patients prospectively.

The main strength of the present study is the fact that a single observer evaluated the patients at disease onset, diagnosed them using Bird *et al*. criteria, and performed most of the follow-up examinations. As a consequence, the method used to classify, inquire and examine the patients was the same throughout the study period. Additional good points are the same geographical area of provenience of the patients, the long follow-up for outcome evaluation, and the detailed clinical examination. A weakness of the study is the long period of enrolment of PMR patients, which spanned over 24 years. In fact, there are data suggesting that PMR and GCA incidence peaks with some variability in succeeding years (12) and that these peaks may not occur in the same season. However, it is impossible to collect a high number of patients from the same geographical area in a short period of time, if the same strict criteria are followed. A study with this aim, published only in abstract form, was performed in Minnesota and showed an increased incidence of PMR in Spring, at least during the years 2000-2014 (13). This study was based on population data obtained over 44 years, a very long period, and lacked the precision of clinical assessment realised in our study. Another limitation, inherent to the design of our study, is the fact that its results cannot be generalised beyond Liguria (Italy).

A further aspect of seasonality influence on rheumatic diseases has been recently indagated in a nation-wide study in South-Korea (14). In that study, the month of birth influenced the subsequent development of several conditions, including PMR, which incidence was higher in subjects with birth during the Spring season.

The main finding of the present study is that in Autumn we found a higher incidence of PMR onset in the subset of patients with concomitant TA. Furthermore, patients with PMR onset in Autumn also has a greater risk of developing TA during the follow-up. This last observation is more intriguing and has not been previously reported. Even if most of the patients who experienced a relapse as TA (9/17) had not had a previous history of TA, this result was not confirmed by multiple regression. Conversely, this analysis showed that MTX use was significantly more frequent in patients with disease onset in Autumn. MTX is used in PMR patients with more severe disease, when therapy is expected to exceed the usual duration, as well as in patients who have contraindications to GC, GC-related side-effects or are resistant to the usual GC dosage (15). Therefore, MTX administration is an indirect indicator of the more severe forms of PMR, including those associated with TA. A hypothesis is that vasculitis rather than PMR by itself could be associated with seasonality.

Among possible explanations for the seasonality of TA in PMR patients, we should take into consideration infection, for different viruses, such as human papilloma virus (16), parvovirus B19 (17), and varicella zoster virus (VZV) (18) have been recently associated with TA; on occasion, viral changes have been seen in biopsy specimens from the temporal artery. Nonetheless, these data have been not confirmed with sufficient consistency. Another possible explanation is that UV light exposure could trigger an immunological response in the superficial arteries of genetically predisposed patients (6). A reasonable time lag between sun exposure in the warmer months and the onset of TA could explain the Autumn peak.

In conclusion, we have demonstrated an increased incidence of PMR in association with TA in patients with PMR onset in Autumn. A risk factor with seasonal variation may be implied in the pathogenesis of this subset of PMR. Analysis of the association between seasonality of onset, season-related environmental conditions, and the onset and progression of PMR and GCA could help understanding the underlying disease mechanisms.

References

1. GUGGINO G, FERRANTE A, MACALUSO F, TRIOLO G, CICCIA F: Pathogenesis of polymyalgia rheumatica. *Reumatismo* 2018; 70: 10-17.
2. GONZÁLEZ-GAY MA, MATTESON EL, CASTAÑEDA S: Polymyalgia rheumatica. *Lancet* 2017; 390: 1700-12.
3. ELLING P, OLSSON AT, ELLING H: Synchronous variations in the incidence of temporal arteritis and polymyalgia rheumatica in Danish counties. Association with epidemics of Mycoplasma pneumonia infection. *J Rheumatol* 1996; 23: 112-9.
4. ALVAREZ-LAFUENTE R: Human parvovirus B19, varicella zoster virus, and human herpes virus 6 in temporal artery biopsy specimens of patients with giant cell arteritis: analysis with quantitative real time polymerase chain reaction. *Ann Rheum Dis* 2005; 64: 780-2.
5. DUHAUT P, BOSSHARD S, CALVET A *et al*.: Giant cell arteritis, polymyalgia rheumatica, and viral hypotheses: a multicenter, prospective case-control study. Groupe de Recherche sur l'Artérite à Cellules Géantes. *J Rheumatol* 1999; 26: 361-9.
6. O'BRIEN JP, REGAN W: Actinically degenerated elastic tissue is the likely antigenic basis of actinic granuloma of the skin and of temporal arteritis. *J Am Acad Dermatol* 1999; 40: 214-22.
7. PRYSHCHEP O, MA-KRUPA W, YOUNGE BR, GORONZY JJ, WEYAND CM: Vessel-specific toll-like receptor profiles in human medium and large arteries. *Circulation* 2008; 118: 1276-84.
8. CIMMINO MA, CAPORALI R, MONTECUCCO CM, ROVIDA S, BARATELLI E, BROGGINI M: A seasonal pattern in the onset of polymyalgia rheumatica. *Ann Rheum Dis* 1990; 49: 521-3.
9. HYSA E, SOBRERO A, CAMELLINO D *et al*.: A seasonal pattern in the onset of polymyalgia rheumatica and giant cell arteritis? A systematic review and meta-analysis. *Semin Arthritis Rheum* 2020; 50: 1131-9.
10. BIRD HA, ESSELINCKX W, DIXON AS, MOWAT AG, WOOD PH: An evaluation of criteria for polymyalgia rheumatica. *Ann Rheum Dis* 1979; 38: 434-9.
11. HUNDER GG, BLOCH DA, MICHEL BA *et al*.: The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. *Arthritis Rheum* 1990; 33: 1122-8.
12. SALVARANI C, GABRIEL SE, O'FALLON WM, HUNDER GG: The incidence of giant cell arteritis in Olmsted County, Minnesota: Apparent fluctuations in a cyclic pattern. *Ann Intern Med* 1995; 123: 192-4.
13. RAHEEL S, CROWSON CS, MATTESON EL: Seasonal variation in incidence of giant cell

arteritis: a population-based cohort study [abstract]. *Arthritis Rheumatol* 2018; 70 (Suppl. 10).
14. LEE J, KIM JH, CHUNG MK *et al*.: Effects of birth months on rheumatic diseases in South Korea: a nationwide case-control study. *Clin Exp Rheumatol* 2020; 38: 411-19.
15. CAMELLINO D, DEJACO C: Update on treatment of polymyalgia rheumatica. *Reumatismo* 2018; 70: 59-66.
16. MOHAMMADI A, PFEIFER JD, LEWIS JS JR: Association between human papillomavirus DNA and temporal arteritis. *BMC Musculoskelet Disord* 2012; 13: 132.
17. ALVAREZ-LAFUENTE R, FERNÁNDEZ-GUTIÉRREZ B, JOVER JA *et al*.: Human parvovirus B19, varicella zoster virus, and human herpes virus 6 in temporal artery biopsy specimens of patients with giant cell arteritis: analysis with quantitative real time polymerase chain reaction. *Ann Rheum Dis* 2005; 64: 780-2.
18. SAMMEL AM, SMITH S, NGUYEN K *et al*.: Assessment for varicella zoster virus in patients newly suspected of having giant cell arteritis. *Rheumatology* (Oxford) 2020; 69: 1992-6