To the Editor:

Polymyalgia rheumatica (PMR) is considered the commonest inflammatory rheumatological disease in adults aged greater than 65 years. Classic symptoms are bilateral pain, aching and stiffness in the shoulders, pelvic girdle and neck, usually with sudden onset. In most cases the patient remembers the exact day when these symptoms appeared. As opposed to the symptoms of osteoarthritis, the stiffness and pain tend to be bilateral or symmetric and improve with activity. They are greater in the morning and improve during the day. The dramatic response to low-dose corticosteroid treatment (15 mg/day prednisone or prednisone equivalent, on average) is characteristic and represents an important diagnostic criterion, despite the recent classification criteria proposed by European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) collaborative group. In some patients, it is necessary to change the initially used glucocorticoid with a different one at equivalent dosage to obtain an effective response.

The management of PMR is generally possible in a rheumatologic outpatient clinic without hospitalization. The relationship between PMR and cancer is still uncertain, and the data available in the literature are contradictory. Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) is an uncommon elderly-onset rheumatic condition, described for the first time by McCarty et al. in 1985. RS3PE syndrome is characterized by tenosynovitis of extensor tendons at the wrist and (less frequently) at the feet that characteristically respond to low-dosages of corticosteroids. Its removal occurs rapidly and relapse is extremely rare in the “benign” forms. Since 1985, cancer and benign tumors have been described in association with RS3PE. RS3PE can represent a neoplastic marker in elderly patients with rheumatic diseases in up to 20% of cases. The levels of vascular endothelial growth factor (VEGF), a cytokine able to increase vascular permeability and dilation, are significantly higher in RS3PE patients than in controls, and the levels decreased after glucocorticoid treatment. The importance of VEGF in the neoplastic spreading is well-known, but the real importance of VEGF in the paraneoplastic potentiality of RS3PE remains speculative until today. RS3PE can be an initial manifestation of PMR or may occur in its course. It is estimated that no more than 10% of patients with PMR may have an RS3PE syndrome, and some authors think that RS3PE can be considered an integral part of the spectrum of the PMR manifestations.

We have evaluated 200 elderly patients (> 65 years old) with PMR, consecutively observed at our rheumatologic outpatient clinic from 2002 to 2014, with regard to presence/absence of RS3PE and presence/absence of a paraneoplastic syndrome. The diagnosis of PMR was made, until 2013, using the criteria proposed by Healey and, after 2013, using the criteria proposed by the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR). The minimum observation time for the appearance of an eventual cancer has been of 24 months from initial diagnosis of PMR. The lack of response to corticosteroid therapy and/or the appearance of signs or symptoms not consistent with typical PMR have shown to be warnings for finding eventual cancer. In the same cohort of patients, the presence of RS3PE syndrome was highlighted in a binary way (yes / no): the fact that the RS3PE is a manifestation of onset or appears during the course of PMR in addition to other clinical manifestations did not constitute an element of assessment. The occurrence of cancer was compared between patients with PMR without RS3PE and those with PMR + RS3PE.

The presence of RS3PE was observed in only seven patients with PMR (3.5%). In three of the seven patients with RS3PE associated with PMR (5 M, 2 F) it was possible to recognize a tumor: prostatic cancer, vesical cancer, multiple myeloma (Table 1). In all these patients, RS3PE presented before the discovery of the malignancies. Its reappearance after a short while represented in all three cases an element of strong suspicion. Subsequent diagnostic decisions were indicated by specific signs: significant rise of prostate specific antigen or appearance of hematuria or a monoclonal peak at
protein electrophoresis. In all these patients, the treatment of neoplasias caused the total and permanent disappearance of RS3PE syndrome. No recurrence was observed during follow-up. In 193 PMR without RS3PE patients, only in two cases did PMR have a paraneoplastic manifestation: in the first case of a neuroendocrine tumor gastric gastrin-secreting; in the second case of a non-Hodgkin lymphoma. In the first case (man 67 years old), a concomitant macrocytic anemia was the key to reaching this final diagnosis.\(^{17}\) When the two groups (PMR without RS3PE vs. PMR + RS3PE) were compared (Table 2), the disease duration of PMR before the diagnosis of cancer was, in the first group, double that in the second group. There is no significant difference with respect to age of onset, ESR, and CRP. Females are much more represented in the second group than the first, confirming the fact that RS3PE syndrome is much more common in males, while the PMR alone is more frequent in females.

The relationship between PMR and neoplasia is still controversial. Several studies have evaluated this question,\(^{3,18,19,20,21}\) but according to our best knowledge, there are no studies that have considered rheumatologic outpatient clinic database. The association of giant-cell arteritis (GCA) and its specific role represents one of the different critical elements.\(^{22,23}\) In our cohort, we evaluated patients with PMR without GCA. RS3PE syndrome represents an uncommon clinical picture which can be associated with malignancies, most often presenting before the discovery of a neoplasia. In a very recent meta-analysis of 331 cases of RS3PE, malignancy was reported in 54 cases (16.31%), but a concurrent rheumatologic condition was reported in only 22 cases (6.65%) and a concurrent PMR in only anecdotal cases.\(^{24}\) This percentage is not much different from the average malignancy rate estimated to be 20% in a pooled data of 64 patients with RS3PE.\(^{10}\) Even in this case, RS3PE associated with PMR accounted for a very small minority. The scarcity of our series is certainly a limitation, as well as its having come from a single centre, but the fact that the RS3PE syndrome is infrequent\(^{10}\) and that the association between RS3PE, PMR, and cancer is not frequently described in the literature,\(^{24}\) must be highlighted.

As is well-known, the term “paraneoplastic syndromes” includes all the various symptoms not attributable to direct tumor invasion or compression.\(^{25}\) It is estimated that paraneoplastic syndromes affect up to 8% of patients with cancer.\(^{26}\) So the much higher percentages observed in patients with RS3PE syndrome warrant attention in paraneoplastic direction. In our experience, RS3PE is rarely associated with PMR (3.5%). The presence of this syndrome in patients with PMR, however, is associated with a very high risk for cancer (28.5% PMR + RS3PE vs. only 2.04% PMR without RS3PE). The repercussions of cancer risk in the elderly with PMR + RS3PE syndrome on health policies are easily understandable. Data from other rheumatologic outpatient clinics and multicentre series are necessary.

**CONFLICT OF INTEREST DISCLOSURES**

The authors declare that no conflicts of interest exist.

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**TABLE 1.**

Baseline characteristics of the three patients with PMR+RS3PE + neoplasia

| Gender, n (%) | Men 2 (66.6%) | Woman 1 (33.3%) |
|---------------|---------------|-----------------|
| Age at the date of examination | 72 yrs (66–79) |
| ESR – median (min-max) [mm/h] | 72.3 (60–80) |
| CRP – median (min-max) [mg/L] | 31.13 (15.9–54.8) |
| Disease duration before the diagnosis of cancer – median (min-max) [months] | 8 (3–10) |

ESR = erythrocyte sedimentation rate; CRP = C- reactive protein.

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**TABLE 2.**

Cancer in PMR+RS3PE vs. PMR-RS3PE: comparison features

| PMR+RS3PE: n. 3/7 | PMR - RS3PE: n. 2/193 |
|-------------------|----------------------|
| Gender, n (%) | Men, 2 (66.6%) | Men, 63 (32.1%) |
| Gender, n (%) | Female, 1 (33.3%) | Female, 130 (67.9%) |
| Age at the date of examination, median (min-max) | 72 yrs (66–79) | 69 yrs (65–91) |
| ESR – median (min-max) [mm/h] | 72.3 (60–80) | 74 (30–105) |
| CRP – median (min-max) [mg/L] | 31.13 (15.9–54.8) | 33.1 (6–34) |
| Disease duration before the diagnosis of cancer, median (min-max) [months] | 8 (3–10) | 16 (12–20) | \(p = .000\) |

ESR = erythrocyte sedimentation rate; CRP = C- reactive protein.
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