Clinical Characteristics of Patients with Remitting Seronegative Symmetrical Synovitis with Pitting Edema Compared to Patients with Pure Polymyalgia Rheumatica

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ABSTRACT. ***Objective.*** To compare clinical features of patients with remitting seronegative symmetrical synovitis with pitting edema (RS3PE) and patients with polymyalgia rheumatica (PMR) and to explore the purported association between RS3PE and malignancy.

Methods. We did a retrospective chart review of patients with RS3PE and PMR treated in a community-based hospital between January 2000 and December 2009. Outcomes assessed were clinical course of disease and associated malignancies.

Results. We identified 28 patients with RS3PE and 123 with pure PMR. All patients with RS3PE fulfilled PMR criteria as well. Age, comorbidity, erythrocyte sedimentation rate, duration and progression of symptoms, treatment response to initial low-dose steroids, and steroid complication rates were similar in both groups. Patients with RS3PE were more likely to be male (79% vs 41%; p = 0.001) and to have a history of smoking (39% vs 15%; p = 0.008) and a higher rate of depression (11% vs 2%; p = 0.044) at diagnosis. Among those with RS3PE, hip pain was less common (39% vs 74%; p = 0.001) than in the PMR group. No patients with RS3PE and 6 patients with pure PMR (4.9%) developed another rheumatological disease during followup. Seven of 9 patients (78%) with concurrent cancer presented slightly more frequently with systemic symptoms compared to patients without cancer (48%; p = 0.098), especially with fatigue (56% vs 22%; p = 0.037) and anorexia (33% vs 9.0%; p = 0.047). Despite rigorous cancer screening in patients with RS3PE, however, the rate of associated malignancy was not statistically different from that of patients with pure PMR [2 (7%) vs 7 (6%), respectively; p = 0.673].

Conclusion. Despite evidence that RS3PE is clinically distinct from PMR, we observed characteristics, treatment response, and outcomes like those expected in pure PMR. Compared to patients with pure PMR, patients with RS3PE are more likely to be male, to be depressed, and to smoke. Contrary to earlier studies, no clear association of RS3PE with malignancy was found despite rigorous cancer screening, although clinicians should be aware that patients with concurrent cancer may manifest more systemic signs and symptoms, as well as steroid resistance. (First Release Dec 15 2011; J Rheumatol 2012;39:148–53; doi:10.3899/jrheum.110558)

Key Indexing Terms:

REMITTING SERONEGATIVE SYMMETRICAL SYNOVITIS WITH PITTING EDEMA
POLYMYALGIA RHEUMATICA PARANEOPLASTIC SYNDROME

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Accepted for publication September 8, 2011.

In 1985, McCarty and colleagues first described remitting seronegative symmetrical synovitis with pitting edema (RS3PE) as a distinct form of seronegative rheumatoid arthritis (RA)-like polyarthritis that primarily affects elderly men[1,2]. It is characterized by symmetrical distal synovitis, marked pitting edema of the dorsum of the hands and/or feet (Figures 1 and 2), absence of rheumatoid factor (RF), and an excellent response to corticosteroids, resulting in longterm remission. Additional case reports have since been published[3,4,5], with cases of unilateral hand involvement also being described[6]. This syndrome has also been described in association with other rheumatological diseases including temporal arteritis, spondyloarthropathies, and Sjögren's syn-

Figure 1. Hand of a patient with remitting seronegative symmetrical synovitis with pitting edema shows excess accumulation of serous fluid.

Figure 2. Characteristic symmetrical distal synovitis and edema of the dorsum of the hands.

drome (SS), but most frequently with late-onset RA and polymyalgia rheumatica (PMR)[7,8,9,10,11,12,13,14,15,16]. As Healey commented[5], the intriguing question is whether RS3PE syndrome, PMR, and seronegative RA are different manifestations of the same benign synovitis.

RS3PE has also been described as a paraneoplastic condition[17,18,19,20,21,22]; however, this association is confounded by advanced age and remains controversial.

The aim of our retrospective study was to compare clinical laboratory features of patients presenting with RS3PE and PMR, in particular by evaluating the rate of development of other rheumatological disease and malignancy during followup.

MATERIALS AND METHODS

In order to identify patients with newly diagnosed RS3PE and PMR, we did a retrospective chart review in a large, community-based teaching hospital in Chiba, Japan, between January 2000 and December 2009. Diagnosis of RS3PE was based on (1) bilateral pitting edema of hands and/or feet at presentation; (2) sudden onset of polyarthritis; (3) age ≥ 50 years; and (4) absence of RF. Diagnosis of PMR was based on Hunder's criteria[23]: (1) age ≥ 50 years; (2) bilateral aching and morning stiffness (≥ 30 min) for at least 1 month involving at least 2 of these 3 areas: neck or torso, shoulders or proximal regions of the arms, and hips or proximal aspects of the thighs; and (3) erythrocyte sedimentation rate (ESR) ≥ 40 mm/h by Westergren method. Patients who met 2 of the 3 criteria and who had a prompt response to corticosteroid therapy were also included[23]. Patients who met criteria for both PMR and RS3PE were included in the RS3PE group. Patients with symptoms that could be attributed to the presence of other diseases, such as active RA, were excluded. Patients presenting with possible giant cell arteritis were similarly excluded. Patients diagnosed with another rheumatologic disease during the study period were discontinued from further followup, although not excluded from our study.

The complete inpatient and outpatient medical records of enrolled patients were reviewed, and information was collected regarding clinical manifestations, laboratory findings (including ESR, hemoglobin, and C-reactive protein levels), types of treatment, and disease course. Depression was identified based on the clinical diagnosis of the treating physicians. Both current and past smokers were considered smokers, due to the absence of detailed smoking status information in this retrospective study. When available, results were recorded for upper and lower gastrointestinal (GI) endoscopy, chest computed tomography (CT), abdominal CT or ultrasound, breast imaging, screening gynecological examination, and prostate-specific antigen (PSA) testing. The definition of paraneoplastic phenomenon required a diagnosis of concurrent cancer occurring < 1 year before or after the diagnosis of RS3PE or pure PMR. Relapse was defined as an exacerbation of PMR/RS3PE symptoms at least 30 days after the incidence date, accompanied by an increase of ESR > 30 mm/h or CRP > 0.5 mg/dl (latex immunagglutination assay). Recurrence was defined by the same criteria as above after the discontinuation of therapy. Patients were considered to be in permanent remission if therapy was discontinued without recurrence of symptoms during the entire followup period.

The clinical course of the disease was assessed by duration of treatment, outcome at the time of analysis, complications of treatment, development of other rheumatological disease, and associated malignancies. For statistical

analysis, Fisher's exact test was used for comparing categorical data and Student's t test for comparing continuous data. Two-tailed p value < 0.05 was considered statistically significant. Stata version 11 (StataCorp., College Station, TX, USA) was used for all statistical analyses.

RESULTS

A total of 151 patients met inclusion criteria, including 28 for RS3PE (male, 79%; mean age, 75 yrs) and 123 for pure PMR (male, 41%; mean age, 74 yrs). All patients with RS3PE also fulfilled the PMR criteria. Baseline characteristics are shown in Table 1. Mean period from diagnosis to final followup was 36 months (range 2–125 mo). Age, comorbidity, ESR, duration, and progression of symptoms were similar in both groups. However, patients with RS3PE were more likely to be male (79% vs 41%; p = 0.001), and to have a history of smoking (39% vs 15%; p = 0.008) and a higher rate of depression (11% vs 2%; p = 0.044) at the time of diagnosis. Among those with RS3PE, hip pain was less common (39% vs 74%; p = 0.001) than in the PMR group. Initial corticosteroid doses, response rate, treatment duration, and steroid complication rate were similar in the 2 groups (Table 2). Except for those who developed another rheumatological illness, no patients in either group required a steroid-sparing agent. Ten patients (36%) with RS3PE and 26 patients (21%) with pure PMR had 1 of the following complications: diabetes, hyperlipidemia, hypertension, avascular necrosis, or infection during the followup period. Although not statistically significant, 7 patients with pure PMR had recurrence compared to none of the patients with RS3PE.

No patients with RS3PE and 6 patients (4.9%) with pure PMR developed another rheumatological disease during the mean followup periods of 30 and 37 months, respectively. Five of these developed RA: 1 developed positive IgM-RF after the initial visit, while 4 remained seronegative. One patient developed antineutrophil cytoplasmic autoantibody-related vasculitis.

Cancer screening was performed more rigorously in patients with RS3PE compared to those with pure PMR: upper GI endoscopy (75% vs 52%, respectively; p = 0.065), colonoscopy (64% vs 42%; p = 0.038), abdominal ultrasound and/or CT (82% vs 52%; p = 0.005), mammography and/or breast ultrasound (18% vs 8%; p = 0.005), gynecologic examination (18% vs 8%; p = 0.005), and PSA screening (39% vs 20%; p = 0.056). This rigorous cancer screening identified malignancy in 2 patients (7%) with RS3PE, and in 7 (6%) with pure PMR (p = 0.673; Table 3).

Seven of 9 patients (78%) who had concurrent cancer presented more frequently with systemic signs and symptoms compared to patients without cancer (48%; p = 0.098), including fever (33% vs 22%; p = 0.48), fatigue (56% vs 22%; p = 0.037), depression (11% vs 3%; p = 0.026), weight loss (11% vs 19%; p = 0.48), and anorexia (33% vs 9%; p = 0.047). Five out of 9 patients with cancer (56% vs 17%; p = 0.007)

Table 1. Demographic and clinical characteristics of patients with RS3PE or pure PMR.

Characteristic, n = 151	RS3PE, n = 28	Pure PMR, n = 123	p
Mean age, yrs	75.0	74.2	0.669
Disease duration until diagnosis, mo	2.2	2.6	0.722
Length of followup, mean, mo	30.0	37.1	0.267
Male, n (%)	22 (78.6)	51 (41.4)	0.001
Smoking, n (%)	11 (39.3)	19 (15.5)	0.008
Diabetes, n (%)	47 (25.0)	22 (17.9)	0.427
Hypertension, n (%)	13 (46.4)	42 (34.2)	0.277
Hyperlipidemia, n (%)	5 (17.9)	22 (17.9)	1.000
Pain and AM stiffness in the following regions, n (%)			
Shoulder	25 (89.3)	110 (89.4)	1.000
Hip/thigh	11 (39.3)	91 (74.0)	0.001
Neck/torso	12 (42.9)	56 (45.5)	0.836
Systemic signs and symptoms*, n (%)	18 (64.3)	57 (46.3)	0.098
Fever ≥ 38°C	10 (35.7)	24 (19.5)	0.080
Malaise or fatigue	5 (17.9)	31 (25.4)	0.471
Depression	3 (10.7)	2 (1.6)	0.044
Weight loss	8 (28.6)	20 (16.3)	0.175
Anorexia	3 (10.7)	12 (9.8)	1.000
ESR ≥ 40 mm/h, n (%)	23 (82.1)	110 (89.4)	0.331
ESR, mm/h†	79.6 ± 33.2	84.4 ± 32.7	0.486
Hemoglobin, g/dl†	11.1 ± 1.5	11.5 ± 1.6	0.263
CRP†, mg/dl, normal range 0.01–0.4	7.1 ± 4.9	8.4 ± 7.2	0.387
IgM-RF			
Tested	28	115	
Positive results, n (%)	0 (0.0)	19 (16.5)	
ACPA			
Tested	17	33	
Positive result	0	0	

* Systemic symptoms and signs were considered positive if 1 of the conditions on the list was present. † Values represent mean ± SD. ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; RS3PE: remitting seronegative symmetrical synovitis with pitting edema; PMR: polymyalgia rheumatica; RF: rheumatoid factor; ACPA: anticitrullinated protein antibodies.

Table 2. Initial treatment and longterm outcome.

Characteristic	RS3PE, n = 28	Pure PMR, n = 123	p
Treatment, n (%)			
NSAID alone	0	2 (1.6)	0.999
CS alone	27 (96.4)	110 (89.4)	0.306
NSAID + CS	1 (3.6)	11 (8.9)	0.697
Initial CS dose, mg			
Mean (minimum, maximum)	12.0 (5, 20)	13.8 (5, 30)	0.084
Treatment duration, mean, mo	24.4	29.9	0.96
Patients with relapse, n (%)	7 (25)	29 (23)	0.39
Patients with recurrence, n (%)	0 (0)	7 (5.7)	0.35
Patients with CS complication*, n (%)	10 (35.7)	26 (21.1)	0.14

* At least 1 CS (corticosteroid) complication during the followup, including diabetes mellitus, hyperlipidemia, hypertension, avascular necrosis, infection requiring intravenous antibiotics, or upper gastrointestinal bleeding/ulcer. RS3PE: remitting seronegative symmetrical synovitis with pitting edema; PMR: polymyalgia rheumatica; NSAID: nonsteroidal antiinflammatory drugs.

Table 3. Cancer in patients with pure PMR or RS3PE.

Sex/Age, yrs	Diagnosis	Time Interval*, mo	Type of Malignancy	Initial Corticosteroid, mg/day	Response to Corticosteroid
1 F 76	RS3PE	+5	Bladder cancer	10	Good
2 M 85	Pure PMR	+5	CUP	10	Good
3 F 75	Pure PMR	+6	MPD	20	Good
4 F 86	Pure PMR	+1	Uterine cancer	10	Good
5 F 71	Pure PMR	–5	Paget's disease	20	Good
6 M 80	Pure PMR	–6	Gastric cancer	30	Good
7 F 75	Pure PMR	–4	Carotid body tumor	10	Good
8 M 83	RS3PE	–1	Colon cancer	20	Good
9 F 68	Pure PMR	–10	HCC	30	Good

* Time interval from diagnosis of PMR or RS3PE to malignancy indicated in months (– and + indicate diagnosis of malignancy was given before or after diagnosis of RS3PE or pure PMR, respectively). RS3PE: remitting seronegative symmetrical synovitis with pitting edema; PMR: polymyalgia rheumatica; MPD: myeloproliferative disease; HCC: hepatocellular carcinoma; CUP: cancer of unknown primary origin.

required a moderate dose of corticosteroid (≥ 20 mg/day) for initial treatment.

DISCUSSION

We compared 28 patients with RS3PE to 123 patients with pure PMR. All patients with RS3PE fulfilled PMR criteria as well. Data were similar in the 2 groups for age, comorbidity, ESR, duration and progression of symptoms, treatment response to initial low-dose steroids, and steroid complication rate. Our study also demonstrates the lack of association between malignancy and RS3PE despite rigorous cancer screening, although patients with concurrent cancer showed more systemic signs and symptoms, as well as resistance to low-dose steroids.

A central question is whether RS3PE is a distinct clinical entity or just a variant of PMR. There were no previous reports regarding how many patients with RS3PE fulfill PMR (Hunder's) criteria as well. Our study revealed that all patients with RS3PE met PMR criteria, an unexpected finding. McCarty[1] in his seminal report, and subsequently several other studies of RS3PE[18,22,24,25], did not exclude patients who also met PMR criteria. Similarly, the RS3PE cohort of Bucaloiu, *et al*[26] included RS3PE patients with clinically remarkable dorsal pitting edema of the hands or feet who had first been diagnosed with PMR. Therefore, we included patients who met both RS3PE and PMR criteria into the RS3PE group. Although RS3PE and PMR share several features, they appear to be clinically distinctive. The relatively acute onset of symmetrical inflammation of joints and carpal tunnel syndrome are overlapping features[1,2,3,4,5,23,27]. These conditions are responsive to low daily doses (10–15 mg) of prednisone. However, RS3PE syndrome is more common in men, involving the wrist, carpus, and flexion digitorum tendons disproportionately, and is associated with marked pitting edema of the dorsum of the hand. Typically, there is no evidence of articular erosions on imaging. Prior studies using magnetic resonance imaging (MRI) have confirmed that extensor tenosynovitis is the principal lesion responsible for subcutaneous and peritendinous soft-tissue edema of the dorsal extremities[7,28]. In general, all cases treated remained well without treatment after remission[24,25,26,29]. In contrast, PMR is more common in women, predominantly involving the shoulders and hips[23,27]. The duration of PMR may be considerably longer, often many years, and flares accompanying reduction of prednisone dosage are very common[33]. The clinical and laboratory features of our patients with RS3PE and patients with pure PMR were similar to those published in earlier reports. Our patients with RS3PE, however, were more likely to be male, and to have a history of smoking and a higher rate of depression, and to have less hip pain than the patients with pure PMR.

Previous reports suggest that RS3PE is a syndrome that may represent the late beginnings of other rheumatic diseases, such as RA, spondyloarthropathies, and SS, among others[7,8,9,10,11,12,13,14,15,16,28,34]. The differential diagnosis of dorsal hand edema is summarized in Table 4.

Differentiation between PMR and RS3PE may be difficult, but it could be confirmed by the extension of the synovitis and the presence of pitting edema. However, Salvarani, *et al*, in a retrospective cohort study of 245 patients with PMR[34], reported a prevalence of distal extremity swelling with pitting edema in 19 patients (8%). They concluded that the distal swelling with pitting edema in these patients was a peripheral manifestation of the inflammatory process associated with PMR, most likely due to vigorous tenosynovitis. Cantini, *et al* also reported similarities in demographic, clinical, and MRI findings between RS3PE syndrome and PMR[28]. In our study, all patients with RS3PE fulfilled PMR criteria, although several important differences in clinical characteristics were found. Notably, none of our patients with RS3PE developed any other rheumatological disease; 6 of the patients with pure PMR (4.9%) developed either RA or vasculitis during followup. This may suggest that RS3PE is a specific entity despite fulfilling PMR criteria.

RS3PE has been described in association with both solid tumors and hematological malignancies, suggesting a

Table 4. Differential diagnosis of dorsal hand edema mimicking PMR or RS3PE.

Rheumatologic disease
Rheumatoid arthritis[7,8]
Spondyloarthropathy[7,8]
Sjögren's syndrome[8]
Mixed connective tissue disease
Vasculitis[37]
Relapsing polychondritis[38]
Malignancy
Hematologic
Non-Hodgkin's lymphoma[11,18]
Chronic lymphocytic leukemia[16]
T-cell lymphoma[13]
Myelodysplastic syndrome[16,18]
Solid tumor
Gastric[12]
Colon[12,13,18]
Pancreatic[13]
Prostate[12]
Hepatic[14]
Ovarian[15]
Endometrial[13]
Breast[17]
Lung[13]
Fibrohistocytoma[18]
Cancer of unknown origin[13]
Others
Sacroidosis[33]
Amyloidosis[34]
Complex regional pain syndrome[36]
Bronchiolitis obliterans organizing pneumonia[39]

RS3PE: remitting seronegative symmetrical synovitis with pitting edema; PMR: polymyalgia rheumatica

paraneoplastic etiology[17,18,19,20,21,22,24,25,26,29] (Table 4), although several followup studies of PMR have failed to demonstrate any robust association[27,35,36,37,38]. The first such observation involved RS3PE appearing 4 months prior to non-Hodgkin's lymphoma[17], while Olive, *et al* have since described, among 27 cases of RS3PE, 2 cases of T-cell lymphomas and 1 case of myelodysplastic syndrome discovered in the course of the initial investigation of polyarthritis[24]. The syndrome has also been described in association with solid tumors such as gastric[18], colon[18,19], prostate[18], hepatic[20], and ovarian[21] adenocarcinomas, as well as with undifferentiated carcinomas[19]. A poor response to corticosteroid treatment and a higher frequency of constitutional symptoms have been described as characteristics of patients with underlying malignancy[29]. In contrast, Schaeverbeke, *et al* followed 13 cases of RS3PE for an average duration of 4.6 years without observing any relationship to malignancy[8]. These studies for RS3PE are few and are based primarily on clinical manifestations without thorough cancer screening using endoscopy or imaging. In our institution, given the purported association, we proactively performed aggressive cancer screening in patients with RS3PE to rule out paraneoplastic syndrome. Despite screening, we identified no evidence of increased malignancy in 28 patients with RS3PE compared to 123 patients with pure PMR. This is an important difference compared to previous reports and suggests that, since cancer incidence increases with advanced age, the purported association of RS3PE and malignancy may well be a coincidence.

Studies[19,28] suggested that in the isolated form of RS3PE syndrome, not associated with other rheumatic conditions, systemic signs or symptoms are present in only 9% of patients, in contrast to 50% of those with the paraneoplastic form. In our study, patients with concurrent cancer presented with modestly more systemic signs and symptoms compared to those without cancer, in addition to requiring a moderate dose of corticosteroid (≥ 20 mg/day) for initial treatment. These findings corroborate previous reports.

Our study has several limitations. First, this was a retrospective study: a future prospective study is needed to corroborate these results. Second, because of the study period, we did not use the most recent criteria for PMR, published in 2008[39] and again in 2010[12]. Finally, only a small number of patients with RS3PE were available for our study. Larger prospective studies using newer criteria are warranted.

To our knowledge, this is the first study to compare the characteristics of RS3PE and pure PMR. Although clinically distinct in several respects, in our study, all patients with RS3PE fulfilled PMR criteria and showed an overall similarity in treatment response and outcomes to those expected in pure PMR. In addition, this study demonstrates the lack of association between malignancy and RS3PE despite rigorous cancer screening, although clinicians should be aware that patients with concurrent cancer showed more systemic signs and symptoms and resistance to low-dose steroids. This finding may help prevent unnecessary cancer screening for patients with RS3PE in favor of age-appropriate screening protocols.

ACKNOWLEDGMENT

The authors acknowledge the collaboration of the staff of the Rheumatology Department at Kameda Medical Center.

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