

# Remitting seronegative symmetrical synovitis with pitting edema

A highly treatable disorder, RS3PE must be distinguished from other forms of arthritis and polymyalgia rheumatica to avoid exposing the patient to inappropriate therapy.

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**R**emitting seronegative symmetrical synovitis with pitting edema (RS3PE) was first described as a subset of acute-onset polyarthritis mainly affecting men in the seventh decade of life and identified as a clinical syndrome in 1985.<sup>1</sup> Distinguishing characteristics of RS3PE include symmetrical synovitis that comes on quickly, pitting edema on the back of the hands, lack of rheumatoid factor (RF), and response to a short course of corticosteroids.<sup>2</sup>

RS3PE is rare and often overlooked by the clinician. The symptoms and signs are frequently mistaken for those of other seronegative polyarthritides of the elderly, most notably late-onset rheumatoid arthritis (LORA) and polymyalgia rheumatica (PMR).<sup>3</sup> Misdiagnosis can result in patients being exposed to more intensive therapy over longer periods of time. Thus, despite being rare, RS3PE syndrome, which is highly treatable, should be part of a complete differential diagnosis.

Understanding the differences between RS3PE, LORA, and PMR in terms of patient presentation, diagnostic findings, treatment modalities, and clinical outcomes will better prepare the clinician to make a correct diagnosis.

## LIMB AND GIRDLE PAIN WITH EDEMA IN AN ELDERLY PATIENT

An 81-year-old white man presented to a rheumatology practice for evaluation of a recently diagnosed inflammatory arthritis. Symptoms that began several months prior included bilateral shoulder pain and swelling of the wrists, hands, and ankles with new-onset bilateral lower-extremity pitting edema requiring hospitalization. The patient noted no associated headaches, jaw claudication, or vision changes. Personal medical history was negative as was a family history of autoimmune disease. The patient was taking no medications and had no known drug allergies. He was a nonsmoker.

Results of radiologic studies of the patient's hands and wrists were negative for joint erosions, and an MRI of the shoulders was unremarkable. Laboratory studies revealed an elevated C-reactive protein (CRP) level of 42.2 mg/dL (normal reference range, 0-0.5 mg/dL); assays for antinuclear antibody, RF, and anticyclic citrullinated

peptide antibody were negative. The patient was found to be anemic, however, and subsequent workup led to a diagnosis of chronic lymphocytic leukemia (CLL). Given the diagnosis, the joint complaints were thought to be paraneoplastic in origin, and the man began treatment for the leukemia.

Six weeks after completing therapy for CLL, the patient was still complaining of significant proximal limb and shoulder-girdle pain in addition to pain and swelling of the wrists, hands, and distal lower extremities. Physical examination revealed 2+ pitting edema of the dorsal aspect of his feet extending to the mid-shin. The hips and shoulders demonstrated decreased range of motion, and mild elbow contractures were noted bilaterally. Also present was synovitis of the wrists and hands. The patient was unable to make a fist with either hand. Swelling allowed him to flex



Pitting edema of the hands caused by RS3PE

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and extend his ankles only minimally, and metatarsophalangeal squeeze elicited tenderness.

The differential diagnosis included RS3PE syndrome, paraneoplastic phenomenon, LORA, and PMR, as well as temporal arteritis, ankylosing spondylitis, the spondyloarthropathies, and polyarteritis nodosa.

The patient was started on prednisone 5 mg three times a day for 2 weeks to be followed by 5 mg twice a day. Three weeks later, his symptoms had improved significantly. On physical examination, the synovitis of the wrist and hands had completely resolved, and the edema in the lower extremities had cleared. Laboratory studies revealed a CRP of 0.7 mg/dL and an ESR of 15 mm/h (normal range in patients older than 50 years, 0-20 mm/h in men and 0-30 mm/h in women). Following the completion of 12 months of low-dose corticosteroids, the patient was without recurrence.

### BACKGROUND

McCarty and colleagues first described RS3PE syndrome with 10 cases characterized by symmetrical synovitis in peripheral joints and pitting edema on the dorsum of the hands, primarily affecting the elderly.<sup>1</sup> Ages of the eight male and two female patients ranged from 59 to 82 years. Seven of the 10 patients could pinpoint the onset of disease to the hour. The patients showed little or no benefit from NSAIDs, and radiographic examination revealed no erosions of the affected joints.

Four additional cases with features similar to those of McCarty's original 10 cases were described by Chaouat and Le Parc.<sup>4</sup> All four patients experienced disease onset at an advanced age, and all exhibited symmetrical polysynovitis with distal pitting edema that resolved in 6 to 18 months. Three of the four patients required hospitalization because of their initial disability. As with McCarty's original 10 patients, RF was absent. Chaouat and Le Parc's patients went into remission without use of disease-modifying antirheumatic drugs (DMARDs).

In a subsequent study, Russell, Hunter, Pearson, and McCarty reviewed an additional 13 cases of RS3PE that confirmed the original findings.<sup>5</sup> Ages of the patients (eight men and five women) ranged from 45 to 81 years with a mean of 68 years. All patients had asymptomatic residual flexion contractures of the fingers and wrists and negative results for RF

on latex fixation testing. No erosions were observed on radiographic examination of the affected joints. Use of low-dose corticosteroids resulted in dramatic clinical improvement, and all patients went on to complete remission without relapse.

### DISCUSSION

The term *synovitis* (rather than arthritis) is used in RS3PE because patients present with symmetrical polysynovitis of the joints and flexor digitorum sheaths associated with pitting edema of the dorsum of the hands and feet.<sup>1</sup> Although the etiology of pitting edema is unknown, Olivieri and colleagues note that on MRI, marked extensor tenosynovitis appears to be primarily responsible for the edema affecting the subcutaneous and peritendinous soft tissue.<sup>6</sup>

The presentation of arthritis and edema of the hands and feet is unusual but will often lead the clinician to consider a number of commonly known differentials. Patients often report shoulder-girdle pain as well.<sup>7</sup> When the symptoms are considered together, the clinician will most likely place LORA and PMR high on the list of differentials.

Based on a multicenter study, a team led by Olivé proposed the following diagnostic criteria for RS3PE: patient age older than 50 years; pitting edema of both hands; polyarthritis with sudden onset; absence of RF; and lack of radiographic evidence of joint destruction.<sup>8</sup>

In a comparison of rheumatoid arthritis (RA) and RS3PE syndrome, RS3PE is distinguished by its remitting nature, absence of joint destruction, and negative serology. In the rare case of RA with pitting edema, the edema often occurs unilaterally and in conjunction with seropositivity to RF. Patients with LORA (development of RA after age 60 years) often have large-joint involvement and an elevated ESR.<sup>9</sup> Other distinguishing features of RS3PE include a higher incidence in males than females, persistent seronegativity, and predictable remission.<sup>5</sup> While differentiation can be difficult, dramatic response to low-dose corticosteroids and long-term remission after withdrawal will allow for definitive diagnosis of RS3PE.

RS3PE can also be easily confused with PMR. In a retrospective study of 245 cases of PMR, Salvarani, Gabriel, and Hunder reported the prevalence of swelling with pitting edema in the distal extremities to be 8%.<sup>10</sup> Both PMR and RS3PE are seronegative, seen at an advanced age, and

### KEY POINTS

- Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) is frequently mistaken for late-onset rheumatoid arthritis or polymyalgia rheumatica (PMR). Misdiagnosis of RS3PE will often result in patients being exposed to more intensive therapy over a longer time.
- The term *synovitis* is used in RS3PE because patients present with symmetrical polysynovitis of the joints and flexor digitorum sheaths associated with pitting edema of the dorsum of the hands and feet. Compared with rheumatoid arthritis, RS3PE is distinguished by its higher incidence in males than females, remitting nature, absence of joint destruction, and negative serology.
- Both RS3PE and PMR conditions are seronegative, seen at an advanced age, and respond dramatically to low-dose corticosteroids. Both diseases also may manifest with sudden onset of symptoms and an elevated ESR, but PMR is often seen in females whereas RS3PE is more frequently seen in males. The major distinguishing feature is symmetrical pitting edema.

**TABLE 1. Comparing three polyarthritides affecting the elderly**

	RA	RS3PE	PMR
Onset	Sudden or gradual	Usually sudden	Sudden
Sex	F>M	M>F	F>M
Age at onset	3rd to 5th decade	7th decade	7th decade
Synovitis	Usually severe	Severe	Mild
Pitting edema	Unusual	All (by definition)	None
RF	Positive (80%)	Negative	Negative
HLA association	DR1.4	B7	DR3.4
Remission	Unusual	Predictable (3-36 mo)	Usual (2 y or more)
Response to low-dose steroids	Often incomplete	Dramatic	Dramatic

Key: F, female; HLA, human leukocyte antigen; M, male; PMR, polymyalgia rheumatica; RA, rheumatoid arthritis; RF, rheumatoid factor; RS3PE, remitting seronegative symmetrical synovitis with pitting edema.

Adapted with permission from Russell et al.<sup>5</sup>

respond dramatically to low-dose corticosteroids. In addition, both diseases may manifest with sudden onset of symptoms and an elevated ESR, but PMR is often seen in females whereas RS3PE is more frequently seen in males. The major distinguishing feature is symmetrical pitting edema.<sup>5</sup> Although differentiation from PMR is difficult, both RS3PE and PMR must be included in the differential diagnosis in an elderly patient who develops an acute inflammatory syndrome, morning stiffness, shoulder-girdle pain, and hand edema.

Serum antibodies can also be a distinguishing feature in RA, RS3PE, and PMR. Results of serology are positive for RF in 80% of all RA cases but negative for RF in RS3PE and PMR. Additionally, human leukocyte antigen (HLA) typing is different in all three diseases. In RA, the HLA type is DR1.4, while in RS3PE, it is B7, and in PMR it is DR3.4.<sup>5</sup> Table 1 shows a comparison of RS3PE with RA and PMR.

Some patients with features of RS3PE also have a paraneoplastic disorder associated with solid tumors and hematologic disorders. Researchers have found a higher prevalence of cancer in patients with RS3PE than in patients matched by age and sex living in the same geographic area.<sup>2</sup> While cases of gastric carcinoma have been identified in patients with RS3PE, other paraneoplastic disorders associated with RS3PE include endometrial carcinoma and pancreatic carcinoma.<sup>11-13</sup> In other cases, as with the patient described, RS3PE has been associated with several hematologic malignancies, including chronic lymphoid leukemia; non-Hodgkin lymphoma; acute lymphocytic leukemia; and precancerous disorders, such as myelodysplastic syndromes.<sup>13-15</sup> An appropriate diagnostic workup is required to rule out a paraneoplastic disorder when the diagnosis of RS3PE is being considered.

## CONCLUSION

The prompt recognition of RS3PE is important because of its impact on treatment options. No DMARDs are required for RS3PE; instead, RS3PE is very responsive to low-dose corticosteroids. Distinguishing RS3PE from PMR in older

patients is important in view of the duration of corticosteroid treatment required. Finally, the diagnosis of RS3PE in an older patient should heighten the suspicion of an underlying malignant disease and mandates a thorough evaluation to rule out this possibility.<sup>16</sup> JAAPA

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