

# An unusual case of remitting seronegative symmetrical synovitis with pitting edema: Case report and literature review

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Anne DD Joseph<sup>1</sup> , Thirunavukarasu Kumanan<sup>1</sup>,  
Naarani Aravinthan<sup>2</sup> and Navaneethakrishnan Suganthan<sup>1</sup> 

## Abstract

Remitting seronegative symmetrical synovitis with pitting edema is a rare but well-recognized clinical entity that is easily overlooked due to lack of clinical vigilance. It is classically described as an acute onset of symmetrical tenosynovitis of both upper and lower extremities with pitting edema, mostly noted in elderly population. Young patients with other rheumatological diseases and unilateral involvement had also been reported, but symmetrical remitting seronegative symmetrical synovitis with pitting edema in a young patient is a rare observation. We hereby report a case of a remitting seronegative symmetrical synovitis with pitting edema in a young male affected by no rheumatological diseases in the past, typically fulfilling the diagnostic criteria and well responded to low-dose steroid therapy. The salient features of the present case in terms of age, remitting seronegative symmetrical synovitis with pitting edema possibly related to undifferentiated arthropathy, reactive arthritis, or diabetes mellitus.

## Keywords

Rheumatology/clinical immunology, remitting seronegative symmetrical synovitis with pitting edema, symmetrical, seronegative, pitting edema, young age

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## Introduction

Remitting seronegative symmetrical synovitis with pitting edema (RS3PE), also described as puffy edematous hand syndrome, is a rare rheumatological condition characterized by symmetrical tenosynovitis of the upper and/or lower extremities with acute onset of pitting edema of the dorsa of the hands and thus gives the appearance of “boxing gloves.” High inflammatory markers, negative rheumatoid factor (RF), and prompt response to low-dose steroids are hallmarks of the disease. RS3PE without concomitant malignancies carries an excellent prognosis. RS3PE was first described in 1985 by McCarty,<sup>1</sup> occurs mostly in elderly population, in particular those who are older than 60 years, and is predominantly observed in males (2:1). Initially, it was thought to be a subset of rheumatoid arthritis (RA), but it is now considered as a distinct clinical entity or syndrome.<sup>2</sup> It is known to be associated with other rheumatological diseases and may represent a paraneoplastic syndrome in a variety of hematological and solid organ neoplasms.<sup>3</sup> Although it is known to be a disease of elderly population, it also presents in young age groups, but it is extremely rare.<sup>4</sup>

We hereby report a case of an RS3PE in a young adult and he improved after a course of low-dose prednisolone.

## Case report

This is a case of a 39-year-old male, a known patient with type 2 diabetes mellitus on metformin and gliclazide for 2 years, with optimal glycemic control, presented with a history of fever for 3 days and an abrupt onset of pain and swelling involving both the dorsum of the hands and wrist joints symmetrically. He also noticed pain and swelling in his left knee for 1 week. He was free from back pain, constitutional symptoms, and ankle swelling. He had good appetite and there was no significant history of weight loss. He denied any history of recurrent fever in the past, rashes, chronic

<sup>1</sup>University Medical Unit, Teaching Hospital, Jaffna, Sri Lanka

<sup>2</sup>Rheumatology Unit, Teaching Hospital, Jaffna, Sri Lanka

### Corresponding Author:

Anne DD Joseph, University Medical Unit, Teaching Hospital, Jaffna 40000, Sri Lanka.

Email: anne.rajendrenjoseph@yahoo.com





**Figure 1.** Bilateral symmetrical pitting edema of the dorsum of the hands.

cough, diarrhea, burning micturition, features of urinary out-flow obstruction, urethral discharge, or sexual promiscuity. He had no family history of rheumatological disease or malignancies. He was a non-smoker and non-alcoholic.

On examination, he was a well-built male and his vitals were stable with a blood pressure of 120/80 mmHg, a heart rate of 86 beats per minute, and a temperature of 37 degrees. He had tender pitting edema involving the dorsum of both hands symmetrically. An examination of the joints showed tenderness, warmth, and swelling, suggestive of synovitis with restricted movements in wrists, bilateral metacarpophalangeal (MCP) joint, proximal interphalangeal (PIP) joint, and the left knee. He had no ankle edema, lymphadenopathy, tenderness over the lower back and sacroiliac joints, and features of enthesitis. Rest of the clinical examinations including cardiovascular, respiratory, abdominal, and neurological examinations were unremarkable (initial presentation of the patient is shown in Figure 1).

At this point, RA, seronegative spondyloarthropathy, reactive arthritis, and arthritis related to the chronic infections such as tuberculosis, polymyalgia rheumatica (PMR), and RS3PE were considered as differential diagnosis. The initial investigations were performed to confirm the diagnosis.

His salient clinical and laboratory features are summarized in Table 1. Sonographic examination of both hands and wrists showed features of tenosynovitis with soft tissue edema and joint effusion. X-rays of the hands did not show any erosions and x-rays of the lumbosacral spine and sacroiliac joints were normal.

Further investigations revealed a negative RF (<20 IU/mL), anti-nuclear antibodies (ANAs), and anti-neutrophil cytoplasmic antibodies (ANCA). Anti-cyclic citrullinated peptide antibody (anti-CCP Ab) level was negative. Venereal disease laboratory (VDRL) test and retroviral studies were also negative. Screening for tuberculosis was performed to exclude the possibility of Poncet's disease with three sputum direct smears, chest x-ray was normal, and tuberculin skin

**Table 1.** Summary of clinical and laboratory parameters of the patient.

Clinical features	Present case
Age of onset (years)	39
Sex	Male
Duration (weeks)	2
Joints involved	Bilateral MCP joint, PIP joint, wrist, left knee
Constitutional symptoms	fever
Comorbidities	Type 2 diabetes mellitus
Drugs taken	Metformin and gliclazide
Signs	Diffuse edema in the dorsum of hands and features of synovitis
ESR (mm/first hour)	67
CRP (mg/L)	55.1
Rheumatoid factor	Negative
Anti-CCP antibody	Negative
Ultrasound scan of hands	Tenosynovitis with soft tissue edema
Radiograph of hands	No deformities, erosions, or joint space narrowing
Sonography of the abdomen and pelvis	Normal architecture of solid organs, no lymphadenopathy or tumors
Steroid dose given (mg)	15
Response (weeks)	2
Follow-up (months)	6

MCP: metacarpophalangeal; PIP: proximal interphalangeal; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; CCP: cyclic citrullinated peptide.

test was negative. At this point, the diagnosis of bilateral RS3PE was made.

To evaluate the possible underlying cause and exclude the possible malignancies, other investigations including serum amylase, lactate dehydrogenase (LDH), blood cultures, antistreptolysin O titer (ASOT), thyroid-stimulating hormone (TSH), free T4, and serum uric acid were performed, which were unremarkable. Ultrasonography of the abdomen and pelvis revealed normal size and architecture of the liver, spleen and kidneys; there were no lymphadenopathy or tumors. Blood picture was obtained to exclude the possibility of hematological malignancies, which was normal.

He was treated with both etoricoxib, a selective cyclooxygenase 2 (COX-2) inhibitor, and low-dose oral prednisolone. Initially, he was given 15 mg of prednisolone, which was continued for 2 weeks and then tailed off over the next 2 weeks. He showed a marked improvement clinically and his inflammatory markers returned to normal levels in 4 weeks. He became free of symptoms at 2 months and maintained the remission for 6 months of follow-up.

## Discussion

As McCarty et al.<sup>1</sup> mentioned, RS3PE is a distinct rheumatological condition, which mostly affects elderly males.

The diagnostic criteria were initially defined by Olive et al.<sup>6</sup> which include the age being over 50 years, pitting edema in the dorsum of both hands, sudden onset of polyarthritis, and negativity of RF. Apart from the age of onset, the other diagnostic criteria were met in the present case. In addition, male gender, dramatic response to low-dose steroid treatment (10–20 mg), and remission without any residual sequelae also support the diagnosis. MA Sattar<sup>5</sup> described RS3PE in three young adults who had excellent prognosis with low-dose steroids and none of them had long-term sequelae.

This syndrome can be a “true” RS3PE; however, similar symptoms can mimic or later exhibit other types of rheumatological conditions such as spondyloarthritis or, to a lesser extent, RA, undifferentiated connective tissue disease, vasculitis or PMR, Sjögren’s syndrome, or relapsing polychondritis.<sup>6–8</sup> Other known associations include bronchiolitis obliterans with organizing pneumonia and sarcoidosis.<sup>9,10</sup>

RS3PE syndrome may occur as a paraneoplastic syndrome of various malignancies. It may predate the condition or present simultaneously or after the development of malignancy.<sup>3</sup> It has been described in association with lung, prostate, ovary, endometrium, breast, bladder, gastrointestinal, and hepatocellular carcinomas. Its association has been widely accepted with hematological malignancies such as non-Hodgkin’s lymphoma and chronic lymphoid leukemia.<sup>3</sup>

Although the pathogenesis of the disease is not well known, now various studies postulated the role of the vascular endothelial growth factor (VEGF) as a major contributor to polysynovitis and subcutaneous edema of the extremities, by increasing vascular permeability,<sup>10,11</sup> and some studies showed that the presence of edema is due to delayed lymphatic drainage.<sup>12,13</sup> An association of HLA-B7 with RS3PE was observed in some studies.<sup>1,14</sup> However, its role in inheritance is still not understood.

Since our patient was 39 years old, the possibilities of spondyloarthritis, RA, reactive arthritis, and PMR were considered as the differentials of his polyarthritis. Spondyloarthropathies may present as pitting edema and peripheral arthritis, but usually the swelling is unilateral and involves the lower limbs. Although spondyloarthropathies can initially present only with peripheral involvement, there were no signs of other common manifestations like sacroiliitis, spondylitis, or enthesitis or of any symptoms of extra-articular involvement.

RA was less probable in this case because it is more frequent in women, not commonly associated with edema; in RA, significant morning stiffness and severe serositis with joint erosions are seen and RF is positive in 80% of cases.<sup>15</sup> Although there was a possibility of seronegative RA in this case, the negativity of anti-CCP Ab excluded the diagnosis of RA.

Reactive arthritis due to sexually transmitted diseases and other infections, and enteropathic arthritis associated with inflammatory bowel diseases were excluded by the relevant

history, clinical examination, and investigations. Tuberculosis is a cause for reactive arthritis;<sup>16</sup> more importantly, an association of RS3PE and tuberculosis had been reported in the literature.<sup>17,18</sup> As tuberculosis is endemic in this part of the world, it had been excluded in this case.

There were no manifestations to support the presence of other conditions such as systemic lupus erythematosus, vasculitis, or PMR.<sup>14,15,19,20</sup>

As noted above, RS3PE can present as paraneoplastic syndrome. The history, clinical examinations, and ultrasound scan of the abdomen and pelvis, blood picture, and chest radiograph were normal in this case.

Recent studies showed the association of RS3PE and anti-diabetic medications such as insulin and dipeptidyl peptidase-4 (DPP-4) inhibitor.<sup>21,22</sup> In the present case, our patient was on neither insulin nor DPP-4 inhibitors. But recently K Oyama et al.<sup>23</sup> reported four cases of RS3PE with type 2 diabetes mellitus or impaired glucose tolerance without insulin or DPP-4 inhibitor medication.

RS3PE responds well to non-steroidal anti-inflammatory drugs (NSAIDs), hydroxychloroquine, and low-dose steroids and the remission is well sustained.<sup>1,3,24</sup> But, in the case of associated underlying malignancy, response is poor and treatment of the underlying malignancy is a primary and mandatory step in the management.

## Conclusion

Although RS3PE is mostly seen in elderly population, it can occur in younger age groups. As RS3PE can be associated with other rheumatological diseases and paraneoplastic syndromes, as well as due to the lack of clear diagnostic criteria, it may cause dilemma in formulating differential diagnosis of this syndrome. As RS3PE is rare in young patients, possibilities of other rheumatological illness, common infections, offending drugs, and malignancies should be excluded. An emerging concept of the association of diabetes mellitus and RS3PE should be considered and further studies are required to verify this association. The salient features of the present case in terms of age, RS3PE in this case it is possibly related to undifferentiated arthropathy, reactive arthritis, or diabetes mellitus.

## Declaration of conflicting interests

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## Ethical approval

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## ORCID iDs

Anne DD Joseph  <https://orcid.org/0000-0002-7851-3151>

Navaneethakrishnan Suganthan  <https://orcid.org/0000-0001-7905-6709>

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