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Remitting Seronegative Symmetrical Synovitis with Pitting Edema: A Rare Case Report

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ABSTRACT

Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) is a rare form of inflammatory arthritis which was first reported by McCarty et al in 1985. It usually affects elderly age group with a clinical presentation of symmetrical polyarthritis with pitting edema on the dorsum of hands and feet. Several studies consider RS3PE to be a form of polymyalgia rheumatica and even seronegative rheumatoid arthritis, but the clinical presentation and pathophysiologic mechanisms indicate that it can be a separate entity altogether. The joints involved frequently as developing stiffness include the metacarpophalangeal (MCP), proximal interphalangeal (PIP), wrist, shoulder, knee, ankle and elbows. RS3PE is a disease/syndrome characterized by an acute onset of polyarthritis with pitting edema, negative rheumatoid factor, absence of joint erosions on radiographs, synovitis suggested by USG/MRI, and a good response to low-dose steroids, with a sustained long-term response.

Keywords: Rheumatoid arthritis, RS3PE, synovitis, pitting edema, inflammatory arthritis

Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) is a rare form of inflammatory arthritis which was first reported by McCarty et al in 1985. It usually affects elderly age group with a clinical presentation of symmetrical polyarthritis with pitting edema on the dorsum of hands and feet. The pathophysiology of RS3PE is not understood clearly. Several studies consider RS3PE to be a form of polymyalgia rheumatica (PMR) and even seronegative rheumatoid arthritis (RA), but the clinical presentation and pathophysiologic mechanisms suggest that it can be a separate entity altogether. The joints involved frequently as developing stiffness include the metacarpophalangeal (MCP), proximal interphalangeal (PIP), wrist, shoulder, knee, ankle and elbows.

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CASE REPORT

A 65-year-old female was referred to GBH General Hospital, Udaipur, Rajasthan on August 12, 2020, with the history of low-grade fever for 10 days followed by swelling over left knee, right hand and swelling over bilateral feet since 7 days. Patient also had a history of hysterectomy followed by radiotherapy about 20 years back, records of which were not available and nature of the illness is unknown.

On examination, left knee joint was red and swollen with increased local temperature. There was pitting edema of bilateral lower limbs and also over right hand (Fig. 1). Ultrasonography (USG) of the local parts showed effusion of the left knee joint with synovitis of the joint along with soft tissue edema over bilateral lower limbs and right hand. Arthrocentesis of the knee was done which showed inflammatory arthritis with cytology showing total counts of 6,400 with neutrophils 60%. Other findings included adenosine deaminase 19.8 U/mL, sugar 40 mg/dL, protein 4.5 g/dL (as the joint aspirate report did not have mononuclear cells predominance, the possibility of viral arthritis was ruled out), serum uric acid 4.0 mg/dL, negative rheumatoid factor (RF), normal anti-cyclic citrullinated peptide (anti-CCP) and normal antinuclear antibody (ANA), normal thyroid-stimulating hormone (TSH), anemia with hemoglobin of 7.8 g/dL, WBC 11 × 10^3 cells/mm^3 - $N_{85\%}$, $L_{20\%}$, elevated erythrocyte

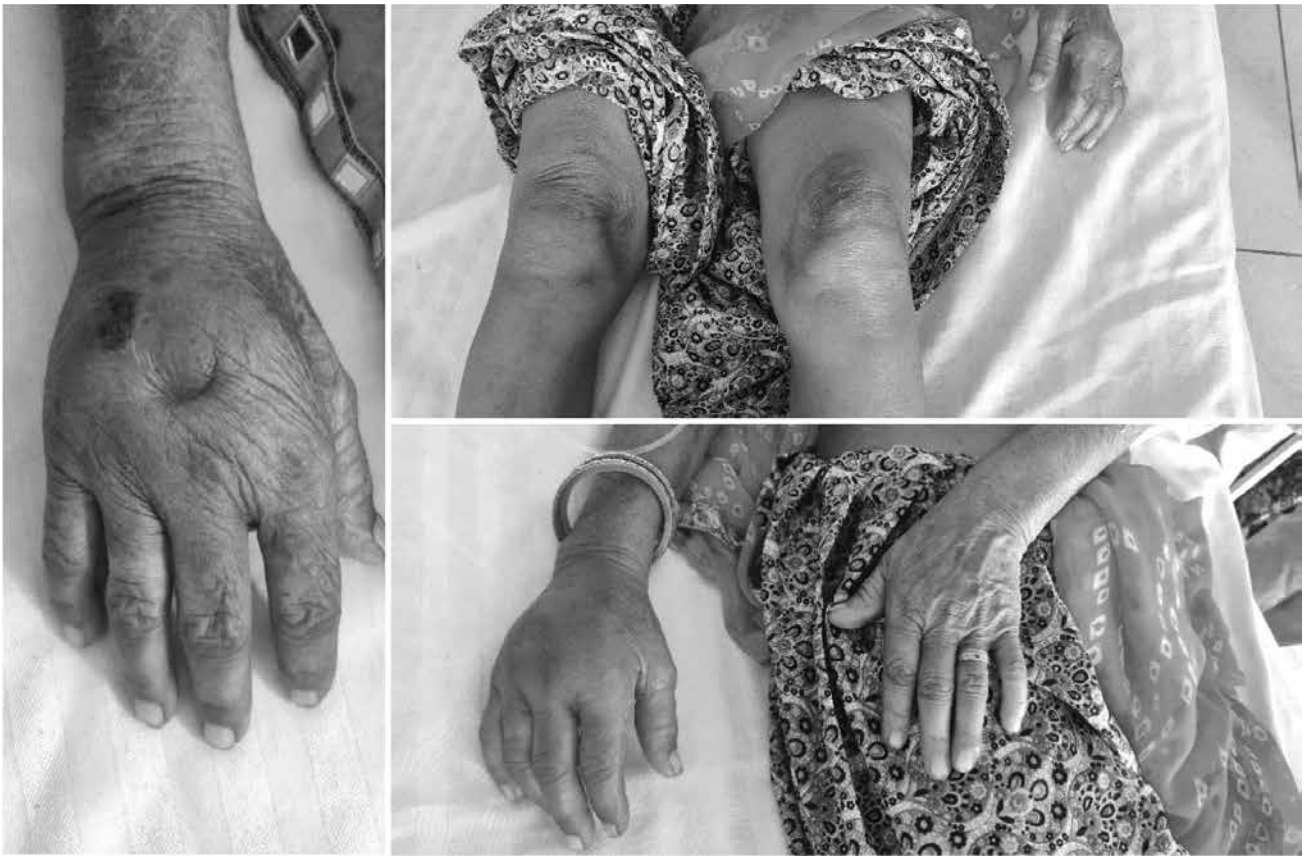

Figure 1. Pitting edema of right hand and swelling over left knee.

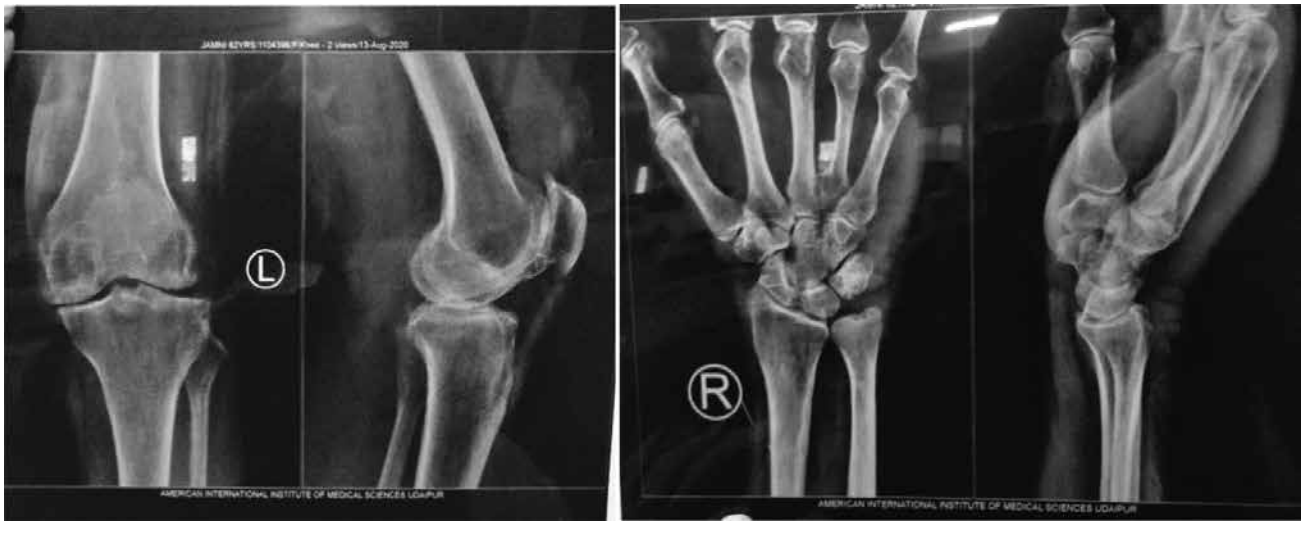

Figure 2. X-ray left knee showing osteoarthritic changes and X-ray right wrist showing soft tissue swelling.

sedimentation rate (ESR) of 111 mm/hr and elevated C-reactive protein (CRP) at 137 mg/L. All other viral markers - human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), anti-HCV (hepatitis C virus) - were negative. X-ray of the affected joints did not reveal any joint erosion. X-ray left knee showed osteoarthritic changes and X-ray right wrist showed soft tissue swelling (Fig. 2). USG of the abdomen showed cholelithiasis of 11 mm and minimal ascites. After ruling out all other causes, patient was started on prednisolone 30 mg. During her brief hospital stay, the patient started responding to treatment, her swelling started reducing and her pain subsided and she was discharged.

DISCUSSION

Remitting seronegative symmetrical synovitis with pitting edema syndrome is defined as seronegative symmetric polysynovitis and arthritis of the distal limbs, primarily the wrist, MCP, PIP and ankle joints with acute onset, together with pitting edema on the dorsum of the hands and feet. Olivé et al evaluated 27 cases with RS3PE retrospectively in 1997 and established the following diagnostic criteria for the disease:

- Clear pitting edema on both hands
- Polyarthritis with acute onset
- Age above 50
- Negative RF.

Nonobservation of erosive or degenerative change in joints and dramatic response to low-dose corticosteroid are characteristic. It is thought that pitting edema, which occurs in distal limbs, develops upon local reaction. RS3PE diagnosis in the presented case was based on the following: Female gender and age >50 years, symmetric pitting edema and sudden-onset polyarthritis, nonobservation of erosion on radiographs, and dramatic and rapid clinical and laboratory response to low-dose corticosteroid treatment within 1 week.

Associations with human leukocyte antigens (HLA) parvovirus B-19 infection malignancy, rheumatologic and autoimmune diseases and increased vascular endothelial growing factor (VEGF) levels have been cited in the etiopathogenesis.

Low-moderate elevation in sedimentation rate has been determined as a laboratory finding in the disease. RF and ANA are negative, while HLA-B7, B22 and B27 tissue antigens may be positive in some patients. Sedimentation rate was moderately increased in our case and RF was negative. Response of RS3PE to nonsteroidal anti-inflammatory drug (NSAID) treatment is not good. Russell et al reported in their series with 13 cases that the patients responded dramatically to 10 mg/day prednisolone treatment. It was found in different case series that remission was ensured in an average of 6-18 months with low-dose steroid treatment. Low-degree flexion contractures that developed on wrists and fingers may sometimes be permanent.

Despite the clear criteria, differential diagnosis of RS3PE is very difficult. Important differential diagnoses include amyloid arthropathy, psoriatic arthropathy, crystal arthropathy, rheumatoid arthritis (RA), late-onset spondyloarthropathies, Reiter syndrome and mixed connective tissue disease; they cause pitting edema on the hands and feet. Reiter syndrome is differentiated by asymmetric stiffness with conjunctivitis and urethritis and asymmetric pitting edema in lower limbs; late-onset spondyloarthropathies are differentiated by asymmetric pitting edema with sacroiliitis; and mixed connective tissue disease is differentiated by Raynaud's phenomenon and ANA positivity in high titer. While having very similar clinical and symptoms, it is distinguished from RS3PE with RF positivity and bone erosions.

RS3PE is most frequently confused with PMR since both are seronegative, are seen in older ages and respond to corticosteroids (Table 1).

Salvarani et al found pitting edema in 8% of the cases in their study examining 245 cases with PMR diagnosis.

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 of onset	3rd to 5th decade	7th decade	7th decade
Synovitis	Usually severe	Severe	Mild
Pitting edema	Unusual	All (as per definition)	No
RF	Positive (80%)	Negative	Negative
HLA association	DR1,4	B7	DR3,4
Remission	Uncommon	Predictable (3-36 mo)	Common (2 y or more)
Response to low-dose steroids	Often incomplete	Dramatic	Dramatic

RA = Rheumatoid arthritis; RS3PE = Remitting seronegative symmetrical synovitis with pitting edema; PMR = Polymyalgia rheumatica; F = Female; M = Male; RF = Rheumatoid factor; HLA = Human leukocyte antigen.

Cantini et al argued that RS3PE may be a precursor or continuance of PMR since inflammation selects the same anatomic target in extra-articular synovial structures in magnetic resonance imaging (MRI) in PMR cases with pitting edema like RS3PE.

However, PMR is a disease mostly seen in women, requiring long-term steroid treatment and showing relapse and recurrence more frequently. In our case, although pain and limitation of motion in the knee joint and ankle joints were present, dramatic response to corticosteroid treatment in very low doses in a short time supports the diagnosis of RS3PE.

Cases diagnosed as RS3PE are observed to suffer from different rheumatologic diseases in the future, including RA, Sjögren's syndrome, spondyloarthropathy and PMR.

Although its diagnostic criteria are clear, RS3PE is a syndrome with a benign course, the differential diagnosis of which is very difficult, and it may lead to rheumatologic and neoplastic diseases. Correct recognition of these cases and patient follow-up after diagnosis are important.

RS3PE responds to relatively small doses of prednisolone. NSAIDs and hydroxychloroquine may provide an added advantage. There is very little role of the disease-modifying antirheumatic drugs (DMARDs). This remission is usually well-sustained. On the other hand, RS3PE with an underlying malignancy responds poorly and treatment of the underlying malignancy is needed as a primary step.

CONCLUSION

RS3PEis a disease/syndrome characterized by an acute onset of polyarthritis with pitting edema, negative RF, absence of joint erosions on radiographs, synovitis suggested by USG/MRI and a good response to low-dose steroids, with a sustained long-term response. A high-degree of suspicion and an early prompt diagnosis is required, as proper treatment results in a dramatic relief to the patient, while misdiagnosis results in a more intensive and expensive therapy, over a long period of time.

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