CASE REPORT

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Remitting Seronegative Symmetrical Synovitis with Pitting Oedema (RS3PE)

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Introduction

Remitting seronegative symmetrical synovitis with pitting oedema (RS3PE) is a rare form of inflammatory arthritis which was first reported by McCarty *et al* in 1985[1]. It usually affects elderly age group with a clinical presentation of symmetrical polyarthritis with pitting oedema 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 and even seronegative rheumatoid arthritis, but the clinical presentation and pathophysiologic mechanisms indicate that it can be a separate entity altogether[2]. The joints involved frequently include metacarpophalangeal (MCP), proximal interphalangeal (PIP), wrist, shoulder, knee, ankle, and elbows[3]. This article presents a case of RS3PE, followed by a brief discussion.

Case report

A 65-year-old lady was referred to GBH General Hospital, Udaipur 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 was unknown.

On examination, the left knee joint was red and swollen with increased local temperature. There was pitting oedema of bilateral lower limbs and over right hand. Ultrasonography of local parts showed effusion of the left knee joint with synovitis of the joint along with soft tissue oedema 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/mm^3 with neutrophils 60% , ADA 19.8 U/L, sugar 1.0 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) normal Anti-Nuclear Antibody (ANA), normal Thyroid-Stimulating Hormone (TSH), haemoglobin of 7.8 g/dl, WBC (11*10^3/mm^3 N: 85%, L: 20%). elevated erythrocyte sedimentation rate (ESR) 111 mm/hr and elevated C-Reactive Protein (CRP) 137 mg/l. All other viral markers HIV, HBSAG, ANTIHCV were negative. X-ray of the affected joints did not reveal any joint erosion. Ultrasonography of the abdomen showed cholelithiasis of 11 mm and minimal ascites. After ruling-out all other causes, the patient was started on prednisolone 30 mg. During her brief hospital stay the patient started responding to treatment, her swelling started reducing and pain subsided and she was discharged.

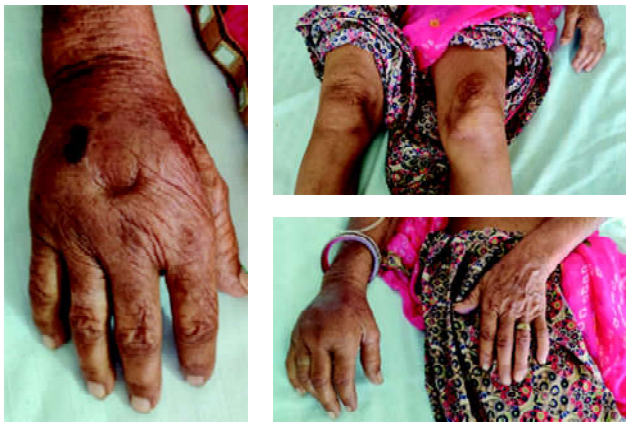

Fig. 1: *Showing pitting oedema of right hand and swelling over left knee.*

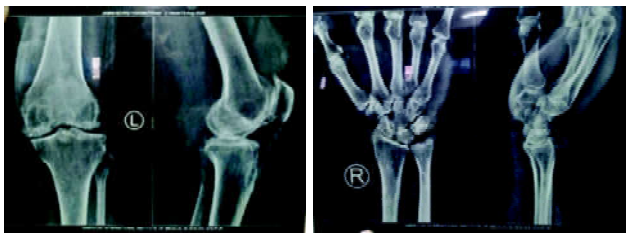

Fig. 2: *X-ray of left knee showing osteoarthritic changes. X-ray of right wrist showing soft-tissue swelling.*

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Discussion

Remitting, seronegative, symmetric synovitis with pitting oedema 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 oedema on the dorsum of the hands and feet[1]. Olive *et al*[4] evaluated 27 cases with RS3PE retrospectively in 1997 and established the following diagnostic criteria for the disease:

- Clear pitting oedema on both hands.
- Polyarthritis with acute onset.
- Age above 50.
- Negative rheumatoid factor[4].

Non-observation of erosive or degenerative change in joints and dramatic response to low-dose corticosteroid are characteristic[3]. It is thought that pitting oedema, which occurs in distal limbs, develops as a local reaction[1]. RS3PE was diagnosed in the presented case was based on the following: Female gender, age > 50 years, symmetric pitting oedema and sudden-onset polyarthritis, non-observation of erosion on radiographs, and rapid clinical and laboratory response to low-dose corticosteroid treatment within one week.

Associations with HLA[1], parvovirus B-19 infection[5], malignancy[3], rheumatologic and autoimmune diseases[6] and increased vascular endothelial growing factor (VEGF) levels[7] have been cited in the etiopathogenesis.

Low-moderate elevation in sedimentation rate has been determined as a laboratory finding in the disease. RF and antinuclear antibodies (ANA) are negative, while HLA-B7, B22 and B27 tissue antigens may be positive in some patients[8,9]. Sedimentation rate was moderately increased in our case and RF was negative. Response of RS3PE to NSAID treatment is not good[1]. Russell *et al*[10] reported 13 cases that patients responded dramatically to 10 mg/day prednisolone treatment. In this case series it was seen that remission was achieved in an average of 6 - 18 months with low-dose steroid treatment[9,10]. Low degree flexion contractures that developed on wrists and fingers may sometimes be permanent. Recurrence may not occur or may be seen between 18 months and 12 years[1,8].

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 oedema on the hands and feet)[11]. Progressive swelling and non-recovery with treatment in amyloid arthropathy, typical skin findings in psoriatic arthritis, and determination of chondrocalcinosis radiologically and crystals in synovial fluid in crystal arthropathy are useful distinctions. Reiter syndrome is differentiated by asymmetric stiffness with conjunctivitis and urethritis and asymmetric pitting oedema in lower limbs; late-onset spondyloarthropathies are differentiated by asymmetric pitting oedema with sacroiliitis; and mixed connective tissue disease is differentiated by Raynaud's phenomenon and ANA positivity in high titer[1,4,9,11]. These were not seen in our case. Asymmetric pitting oedema may be seen in late-onset RA rarely. While having very similar clinical and symptoms, it is distinguished from RS3PE with RF positivity and bone erosions[9].

Remitting, seronegative, symmetric synovitis with pitting oedema is most frequently confused with polymyalgia rheumatica (PMR) since both are seronegative, are seen in older ages and respond to corticosteroids.

Table I: Comparing three polyarthritides affecting the elderly.

	RA	RS3PE	PMR
Onest	Sudden of gradual	Usually sudden	Sudden
Gender	F > M	M > F	F > M
Age at onset	3rd to 5th decade	7th decade	7th decade
Synovitis	Usually Severe	Severe	Mild
Pitting oedema	Unusual	All (by definition)	None
RF	Positive (80%)	Negative	Negative
HLA Association	DR4	B7	DR3.4
Remission	Unusual	Predictable (3 - 36 mc)	Unusual (2 y or more)
Response to low-dose steroids	Often incomplete	Dramatic	Dramatic

Salvarani *et al*[12] found pitting oedema in 8% of cases in their study examining 245 cases with PMR. Cantini *et al*[8] 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 in PMR cases with pitting oedema, like RS3PE.

However, PMR is a disease mostly seen in women, requiring long-term steroid treatment and showing relapse and recurrence more frequently[6-10]. In our case, although pain and limitation of motion in the knee and ankle joints were present, dramatic response to corticosteroid treatment in very low-doses in a short time supports the diagnosis of RS3PE.

Cases of as RS3PE are observed to suffer from different

rheumatologic diseases in the future, including RA, Sjögren's syndrome, spondyloarthropathy, and PMR[1,9,12].

In conclusion, 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 be associated with rheumatologic and neoplastic diseases. Correct recognition of these cases and patient follow-up after diagnosis are important.

Remitting seronegative symmetrical synovitis with pitting oedema responds to relatively small doses of prednisolone. Nonsteroidal anti-inflammatory drugs (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

Remitting seronegative symmetrical synovitis with pitting oedema is a disease/syndrome characterised by an acute onset of polyarthritis with pitting oedema, 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. 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 prolonged and expensive therapy.

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