

Case Report

Idiopathic, remitting, seronegative, symmetrical synovitis with pitting oedema (RS3PE) – an overlooked clinical entity?

Sanchayan Thanancheyan, Ghetheeswaran Srivickneswaran, Nisanthan Selvaratnam, Sivakajani Balakumar

Teaching Hospital, Jaffna, Sri Lanka.

Keywords: remitting seronegative symmetrical synovitis with pitting oedema (RS3PE), polyarthritis, pitting oedema, malignancy

Corresponding Author: Sanchayan Thanancheyan E-mail: <sanchai1990@gmail.com >  <https://orcid.org/0000-0001-6906-385X>
Received: 14 Oct 2020, Accepted revised version: 12 Jan 2021, Published: 31 Mar 2021
Competing Interests: Authors have declared that no competing interests exist

© Authors. This is an open-access article distributed under a Creative Commons Attribution-Share Alike 4.0 International License (CC BY-SA 4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are attributed and materials are shared under the same license.



Introduction

Remitting, seronegative, symmetrical synovitis with pitting oedema (RS3PE) is an uncommon, late-onset, rheumatic syndrome [1] featuring acute onset of polyarthritis with pitting oedema, negative rheumatoid factor (RF), absence of joint erosions on radiographs, synovitis evidenced by imaging and a remarkable response to low-dose steroids, with a sustained response [2]. Pitting oedema is prominent in the dorsum of the hand and foot. Aetiology of RS3PE syndrome is still unknown. Possible associations with human leukocyte antigens (HLA), malignancy, and parvovirus B19 infection have been proposed and cases accompanied by other rheumatoid and autoimmune disorders have been reported raising suspicion of underlying autoimmunity in the pathogenesis of RS3PE syndrome [3]. It is believed to be a paraneoplastic rheumatic disease as it is noted to be associated with a variety of malignancies as well. Vascular endothelial growth factor (VEGF) appears to have a role in the pathogenesis of this disease. Patients with RS3PE, without underlying malignancy, respond well to steroids and carry a good prognosis [1].

This case report describes an elderly male patient with no significant past medical history who presented with pain and swelling of bilateral hands and right foot. His blood investigations showed a neutrophil leucocytosis, raised inflammatory markers and negative autoimmune profile. Age and sex related malignancy screening was negative. X-ray hands and foot showed soft tissue oedema and the absence of joint erosions. Human leukocyte antigen B27 was detected. He was diagnosed to have RS3PE and was treated with a short course of low dose oral prednisolone and showed a dramatic improvement.

Case presentation

A 62-year-old man without any significant medical problems, presented to medical casualty at Teaching Hospital, Jaffna (THJ) with painful swelling of bilateral hands and right foot of 1

week's duration. He did not have joint swelling but there was a history of neck pain and back pain which had settled by the time of admission. He did not have fever or other constitutional symptoms. His urinary and bowel habits were normal.

On examination, he was found to have pitting oedema of the dorsum of both hands and dorsal surface of the right foot (Figure 1). Bilateral metacarpophalangeal (MCP) joints and wrist joints were very tender. Tenderness was also noted in the right ankle joint.



Figure 1: Pitting oedema in dorsal surface of bilateral hands and right foot at presentation

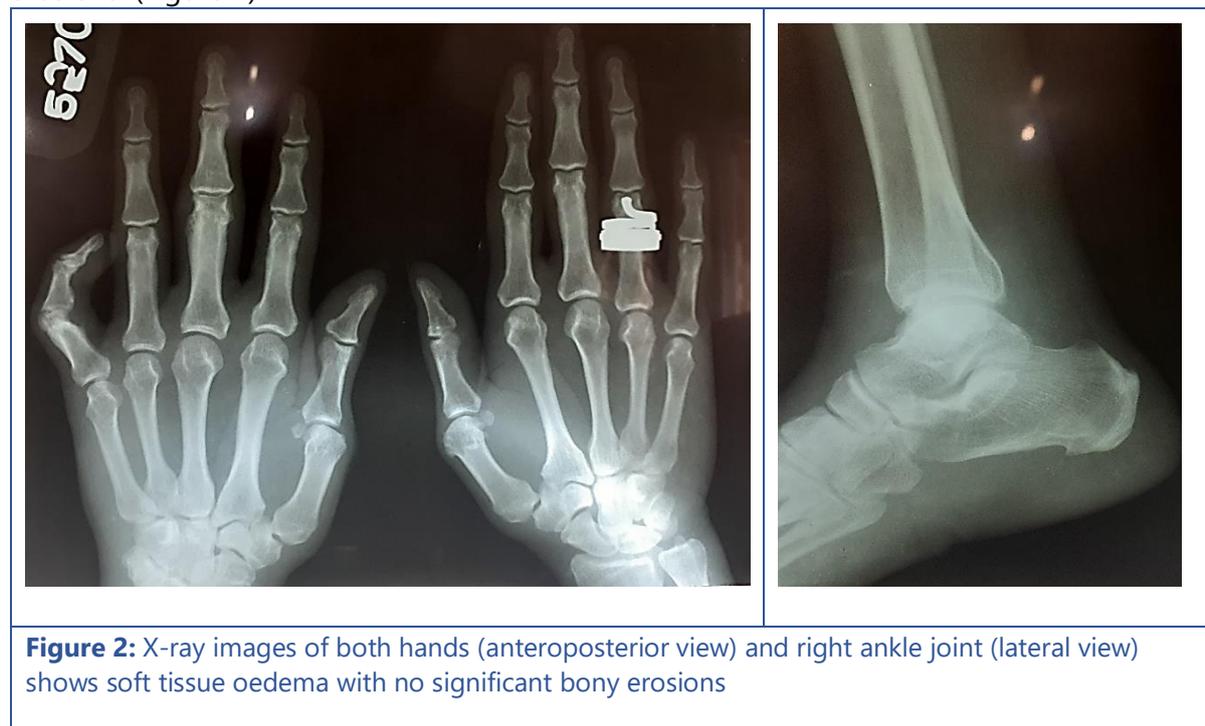
Full blood count (FBC) showed a neutrophil leucocytosis. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were high. Serum uric acid level was not elevated. Both rheumatoid factor (RF) and anti-nuclear antibodies (ANA) were negative. HLA B27 antigen was positive. (Table 1)

Table 1: Summary of investigations

Investigations	Results
Full blood count	White blood cells: 18.23 / μ L (4-10) Neutrophils: 90.2 % Lymphocytes: 6.1% Monocytes: 3.3% Eosinophils: 0.01% Haemoglobin: 12.8 g/dL (13.0-16.0) Platelets: 224/ μ L (150-450)
Liver function test	Alanine aminotransferase: 40 U/L (16-63) Aspartate aminotransferase: 40 U/L (15-37) Alkaline phosphatase: 72 U/L (46-116) Total protein: 66g/L (64-82) Albumin: 29g/L (34-50) Globulin: 37g/L (22-48)
Serum amylase	49 U/L (25-115)
Serum electrolytes	Sodium: 136 mmol/L (136-145) Potassium: 3.3 mmol/L (3.5-5.1) Calcium (Corrected): 2.43 mmol/L (2.01-2.54) Phosphorus: 0.92 mmol/L (0.81-1.45)
Blood urea	2.8 mmol/L (2.5-6.4)

Serum creatinine	80 µmol/L (62-115)
Erythrocyte sedimentation rate	85 mm/1 st hour
C-reactive protein	247 mg/L (0-3)
Post prandial blood sugar	9.79 mmol/L (< 7.77)
Fasting blood sugar	5.13 mmol/L (< 6.10)
Random blood sugar	115 mg/dL
Serum uric acid	187 µmol/L (208-506)
Lactate dehydrogenase	197 U/L (120-246)
Urine full report	Protein: + White Cells: 3-5 Red Cells: Nil Crystals: Nil Casts: Nil
Blood picture	No major morphological abnormalities detected apart from moderate rouleaux
Serum protein electrophoresis	Normal pattern
Rheumatoid factor	Negative
Anti-nuclear antibody titre	Negative 1:80
Prostate specific antigen	Negative
Carbohydrate antigen 19.9	< 1.4 U/ml (0-37)
Human leucocyte antigen B27	Positive

X-rays of both hands and left foot showed soft tissue oedema without evidence of bone erosions. (Figure 2)



2D echocardiogram was normal. Malignancy screening was negative evidenced by normal chest X-ray, normal ultrasonography of abdomen and pelvis and negative tumour markers – carbohydrate antigen (CA) 19.9 and prostate specific antigen (PSA) – serum tumour markers for pancreatic and prostate malignancy respectively.

A clinical diagnosis of RS3PE was made and he was started on low dose oral prednisolone 15mg daily along with oral Ibuprofen 200mg t.d.s and oral paracetamol 1 g t.d.s. He showed dramatic improvement with resolution of oedema and remission of pain. He was subsequently discharged on a tail off regime of oral prednisolone and analgesics.

On subsequent follow up visits, he was found to be symptom free. (Figure 3) Monthly clinic follow-up was arranged at the Rheumatology Clinic at THJ.



Figure 3: Complete resolution of oedema after one week of treatment with steroids and NSAIDs

Discussion

In a study on patients with RS3PE, the mean age of diagnosis was around 72 years (58-92). Sex ratio was found to be 2:1 with male predominance. Major clinical features were polyarthritis and oedema of both hands. MCP joints were mostly affected, followed by proximal interphalangeal joints, wrists, shoulders, knees, ankles and elbows. RF was negative in all patients. ANA was positive at low titre in one third of patients. Erosions were observed in only one patient [4].

In this case, the clinical features were strongly suggestive of idiopathic RS3PE. He was in his sixties and the presentation was pitting oedema of both hands and left foot with severe tenderness over the metacarpophalangeal and wrist joints. X-rays showed only soft tissue swelling without any evidence of erosions. Blood investigations showed elevated inflammatory markers. Serological markers of other rheumatoid diseases (RF, ANA) were negative. HLA B27 antigen was detected. Malignancy screening was negative. He responded well to treatment with low dose steroids. The only atypical feature was the involvement of the left foot, whereas in RS3PE bilateral upper extremity involvement is often observed.

While RS3PE almost always shows symmetrical involvement of the upper extremities, it may rarely manifest as unilateral disease and this protection against the expression of RS3PE in a limb points out a possible role for neural and other local factors in the onset and course of RS3PE [5]. In the most recent studies, involvement of both hands and feet has been reported and unilateral RS3PE is also well-recognized [6]. Although the disease is more prevalent in the geriatric age group, cases in younger people have been reported. In addition, increasing

numbers of female cases are also been reported to challenge the male predominance that was originally described. The common laboratory findings include elevated acute phase reactants (ESR, CRP) favouring an underlying inflammatory process. Rheumatoid factor and anti-citrullinated cyclic peptide (CCP) are typically negative. Anti-nuclear antibodies could be positive but this is uncommon. Varying degrees of anaemia may be present. Radiologically, erosions are classically absent. Imaging (USS/MRI) of the extremities have shown tenosynovitis as a major cause of subcutaneous oedema. A study revealed that extensor tenosynovitis is more common than flexor tenosynovitis. USS-Doppler is now considered to be the favoured modality of radiological evaluation [2].

RS3PE, though earlier considered as a form of late-onset rheumatoid arthritis, has been found to be associated with rheumatic diseases, sarcoidosis, amyloidosis, relapsing polychondritis and bronchiolitis obliterans organizing pneumonia. On the basis of these facts RS3PE is now believed to be a distinct clinical entity [2].

The association of RS3PE with neoplasms is well documented, especially with solid tumours such as lung, prostate, ovary, breast, bladder, endometrium, gastrointestinal tract, hepatocellular carcinoma and haematological malignancies [7]. So, it is mandatory to look for malignancy in patients with RS3PE. In this patient, blood investigations and basic imaging studies did not reveal any hint of underlying malignancies.

The immunopathogenesis of this disease is still unclear. VEGF, by increasing vascular permeability, is considered as the major contributor to polysynovitis and subcutaneous oedema. Interleukin-6 has been found to be high in the synovial fluid of patients. HLA (HLA-B7, HLA-B22, HLA-B27, HLA-A2, HLA-CW7, HLA-DQW2) is found to be associated with RS3PE [7,8]. A definite triggering factor for the development of RS3PE has not been established. Parvovirus, *Streptobacillus* and *Mycoplasma* infection and the Bacillus Calmette-Guerin (BCG) vaccine are suspected as potential triggers [7].

RS3PE responds well to small doses of prednisolone (5-20 mg). Nonsteroidal anti-inflammatory drugs (NSAIDs) and hydroxychloroquine are also useful. There is very little role for the disease-modifying antirheumatic drugs (DMARDs) [9]. The remission is usually well-sustained. But in RS3PE associated with an underlying malignancy, the response is poor, and treatment of the underlying malignancy is the most appropriate treatment [2].

Conclusion

RS3PE should be considered as a differential diagnosis in patients presenting with symmetrical joint pain and oedema of the extremities. Early diagnosis will facilitate prompt treatment with steroids with high rates of remission. Underlying malignancy should be excluded in the setting of RS3PE.

Acknowledgements

We thank the house officers and nursing staff of Ward 09, THJ, for their help in managing this patient. We are also grateful to Dr. A. Narani, Consultant Rheumatologist, THJ for her efforts in establishing the diagnosis.

References

1. Li H, Altman RD, Yao Q. RS3PE: clinical and research development. *Current rheumatology reports*. 2015 Aug 1;17(8):49. <https://doi.org/10.1007/s11926-015-0525-0>
2. Varshney AN, Singh NK. Syndrome of remitting seronegative symmetrical synovitis with pitting edema: A case series. *Journal of Postgraduate Medicine*. 2015 Jan;61(1):38. <https://doi.org/10.4103/0022-3859.147038>
3. Ito E, Okamoto H, Mochizuki A, Ohara K, Kato M, Terashima Y, Tanaka E, Takagi K, Uchiyama S, Iwata M. Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome accompanied by Parkinson's disease. *Internal Medicine*. 2007;46(14):1139-42. <https://doi.org/10.2169/internalmedicine.46.0029>
4. Olive A, Del Blanco J, Pons M, Vaquero M, Tena X. The clinical spectrum of remitting seronegative symmetrical synovitis with pitting edema. The Catalan Group for the Study of RS3PE. *The Journal of Rheumatology*. 1997 Feb 1;24(2):333-6.
5. Keenan RT, Hamalian GM, Pillinger MH. RS3PE presenting in a unilateral pattern: case report and review of the literature. In *Seminars in arthritis and rheumatism* 2009 Jun 1 (Vol. 38, No. 6, pp. 428-433). WB Saunders. <https://doi.org/10.1016/j.semarthrit.2008.03.008>
6. Özşahin M, Ataoğlu S, Turan H. Unilateral RS3PE with young-onset rheumatoid arthritis. In *Seminars in Arthritis and Rheumatism* 2011 (Vol. 4, No. 40, p. e1). <https://doi.org/10.1016/j.semarthrit.2010.09.001>
7. Yao Q, Su X, Altman RD. Is remitting seronegative symmetrical synovitis with pitting edema (RS3PE) a subset of rheumatoid arthritis? In *Seminars in arthritis and rheumatism* 2010 Aug 1 (Vol. 40, No. 1, pp. 89-94). WB Saunders. <https://doi.org/10.1016/j.semarthrit.2008.11.006>
8. Paksoy F, Ulaş T, Mazi EE, Damar AB, Borlu F. Syndrome of remitting seronegative symmetrical synovitis with pitting edema (RS3PE). *Archives of Rheumatology*. 2010;25(2):088-90. <https://doi.org/10.5152/tjr.2010.08>
9. Hartley A J, Manson J, Jawad A S M. (2010, January). Remitting seronegative symmetrical synovitis with pitting edema. *Grand Rounds*, 10, 71-73.
Available at [Remitting seronegative symmetrical synovitis with pitting oedema | Grand Rounds \(grandroundsjournal.com\)](http://Remitting%20seronegative%20symmetrical%20synovitis%20with%20pitting%20oedema%20|%20Grand%20Rounds%20(grandroundsjournal.com)) Accessed 12.01.2021.