RS3PE and the role of ultrasound. A case report and brief review of the literature

Mariaeva Romano, Silvia Sirotti, Georgios Filippou, Piercarlo Sarzi Puttini

Department of Rheumatology, Luigi Sacco University Hospital, Milan, Italy

Abstract

Remitting seronegative symmetric synovitis with pitting edema (RS3PE) is a rare syndrome characterised by acute onset of symmetrical distal synovitis and tenosynovitis, associated with severe pitting edema of the dorsum of the hands and feet, seronegativity for autoimmunity and dramatic response to glucocorticoids.

First described by McCarty *et al*. in 1985, RS3PE is reported mostly in elderly males, but it can also rarely occur in young people.

Although it was initially regarded as a form of rheumatoid arthritis (RA), it is now considered a clinical distinct entity that can be associated with other rheumatologic conditions or be secondary to underlying diseases, such as cancer. As revealed by magnetic resonance imaging (MRI), the typical landmark of RS3PE is extensor tenosynovitis.

Due to extensive subcutaneous edema of the extremities, the clinical assessment of synovitis and tenosynovitis is difficult. On the other hand, the use of MRI is expensive, time-consuming and requires experienced staffs.

Musculoskeletal ultrasound (MSUS) may be a viable, reliable and cost-effective tool for evaluation of RS3PE patients.

We hereby report the case of an 84 year-old woman presenting with bilateral hand and wrist swelling and morning stiffness. Clinical examination, laboratory tests and imaging led to a diagnosis of RS3PE. The aim of this report is to discuss the role of MSUS in RS3PE for the purpose of diagnosis and differential diagnosis compared with other rheumatologic conditions.

Correspondence: Mariaeva Romano, Rheumatology Department, Building 16, 2nd floor, Luigi Sacco University Hospital, via G.B Grassi 74, 20157 Milan, Italy.
Tel.: +39.02.3904.1.
E-mail: mariaeva.romano@hotmail.it

Key words: Remitting seronegative symmetrical synovitis with pitting edema; RS3PE; ultrasonography; imaging.

Contributions: the authors contributed equally.

Conflict of interests: the authors declare no potential conflict of interests.

Received for publication: 24 February 2021.
Revision received: 7 April 2021.
Accepted for publication: 7 April 2021.

©Copyright: the Author(s), 2021
Licensee PAGEPress, Italy
Beyond Rheumatology 2021; 3:61
doi:10.4081/br.2021.61

This article is distributed under the terms of the Creative Commons Attribution Noncommercial License (by-nc 4.0) which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author(s) and source are credited.

Introduction

Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome is a rare inflammatory disease, which commonly occurs in elderly individuals.

It was originally reported by McCarty *et al.* in 1985[1] and is characterized by acute onset of symmetrical synovitis with pitting edema on the dorsum of hands and feet, absence of rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (aCCP). The differential diagnosis could be challenging, as similar manifestations may be present also in other diseases such as elderly-onset rheumatoid arthritis (EORA) or microcrystalline arthritis.

Furthermore, RS3PE can present as a paraneoplastic syndrome of various malignancies, in particular haematological malignancies, but it has been reported also in association with lung, prostrate, breast, bladder, gastrointestinal cancer.[2]

There is conflicting data on the possible association among RS3PE, diabetes mellitus, and anti-diabetic agents.[3]

The pathogenesis of the disease is unknown. Some studies reported an association of HLA-B7,HLA-CW7, and HLA-DQW.[4,5]

Other studies highlighted the role of the vascular endothelial growth factor (VEGF) in generating synovitis and edema due to its role in increasing vascular permeability. The higher serum level of VEGF in RS3PE patients compared to RA patients and healthy individuals may aid in the diagnosis of this syndrome.[6]

Other studies reported the presence of edema with delayed lymphatic drainage.[7]

Classification criteria for RS3PE have not yet been established. Olive *et al*. in 1997 proposed that all the following diagnostic criteria had to be satisfied in order to make a diagnosis of RS3PE: i) pitting edema in all 4 limbs; ii) acute onset; iii) age >50 years; and iv) negative RF.

Patients with this syndrome are typically diagnosed when they present with the aforementioned criteria and when other diseases have been ruled out.[5]

Joint synovitis and tenosynovitis, the landmarks of the disease, can be extremely difficult to assess by clinical examination due to the severe subcutaneous oedema typical of this disease.

Over the last two decades, ultrasound (US) has been increasingly used by rheumatologists for a bed-side approach, in order to support both the diagnostic process and the assessment of the disease state and evolution.[8] US has proved to be sensitive and reliable in revealing many elementary lesions, typical of rheumatic diseases,

Non-commercial use only

such as synovitis, enthesitis, crystal deposition, osteophytes[9-12] leading many rheumatologists to gain more knowledge and invest in US equipment.

We describe a case of an RS3PE in an 84-year-old woman and discuss the contribution of US as diagnostic tool according to available evidence.

Case Report

An 84-year-old woman presented at the outpatient clinic of our hospital for acute swelling and pain of the hands and wrists in the previous 5 days. The patient was diagnosed with polymyalgia rheumatica 2 years earlier. She was treated with steroids and achieved complete remission of symptoms. She discontinued the treatment approximately 6 months before this episode of pain and swelling of the hands. The patient described morning stiffness of both hands and shoulders (for approximately 1 hour). She did not complain any systemic symptoms, cutaneous manifestations, gastrointestinal or urinary symptoms and did not have any traumas.

Her past medical history included arterial hypertension, which was treated with amlodipine 5 mg/day. She had no known drug allergies. There was no family history of connective tissue disease or inflammatory arthritis.

She appeared her stated age and in no apparent distress. Her temperature was 36.5°C, blood pressure 125/85 mmHg, heart rate 74 beats per minutes. Cardiovascular, respiratory, abdominal and neurological examination was unremarkable. There was no lymphadenopathy. The musculoskeletal examination revealed severe pitting edema of both hands and wrists with pain during passive movement of the joints of the hands and wrists (Figure 1). Her shoulder range of motion was decreased during active movement and painful. Her range of motion of the hips was overall preserved with mild pain in the extreme degrees of passive movement. Clinical maneuvers for sacroiliitis were negative.

Ultrasound examination was performed using a Samsung RS080A scanner with a multifrequency linear array transducer (12-18 MHz). The sonography (Figure 2) of shoulders, hands, hips and feet revealed a severe edema of the subcutaneous tissue of both hands (especially on dorsal side) with synovitis of the II, III and IV metacarpal-phalangeal joint bilaterally (Grey scale synovitis grade 2 and power Doppler grade 1 according to the GLOESS scoring system[13]). Mild tenosynovitis of the flexor tendons at both wrists was also observed. There were no erosions in the MCP joints and the extensor tendons of the hands and wrists appeared normal. As to the shoulders, a complete lesion of the supraspinatus was seen bilaterally without any signs of inflammation, while in the hips some bone profile irregularities consistent with hip osteoarthritis were observed, also in this case, without any US signs of inflammation. No signs of crystalline deposition were found in wrists, knees and I metatarsal-phalangeal joints.

Laboratory findings are shown in Table 1. Patient's erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were elevated. The remainder of her laboratory tests was unremarkable.

To exclude any possible neoplasms, prior to the prescription of methylprednisolone, other investigations, including chest X-ray, abdominal ultrasound and mammography, were also performed and were normal. A blood picture test was also performed to exclude hematological malignancies and was normal.

A diagnosis of RS3PE syndrome was made, based on the symmetrical symptom of peripheral pitting edema and on the imaging features that excluded an inflammatory involvement of shoulders and hips and the presence of crystalline deposition in joints or joint erosions. After oral methylprednisolone treatment was initiated (started dose 16 mg/day), she had a rapid response to the steroid with an almost complete resolution of symptoms in a few days; edema and joint pain were disappeared completely in 2 weeks. Her inflammatory markers returned to normal levels in 3 weeks. The steroid was gradually tapered till discontinuation over 3 months. The remission was maintained for a 6 months follow-up. No complications or symptom recurrence occurred over the following 6 months post-treatment initiation.

Discussion and literature overview

RS3PE syndrome is a rare, overlooked, inflammatory syndrome characterized by acute onset of symmetrical synovitis with

Non-commercial use only

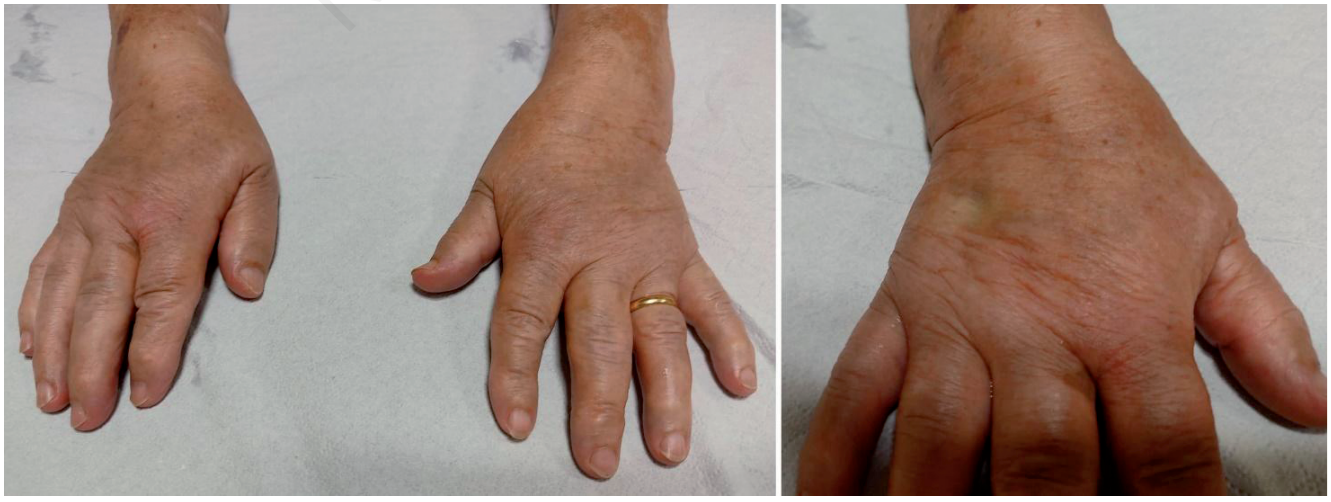

Figure 1. Swelling of hands and wrists with pitting edema.

pitting edema on the dorsum of the feet and hands with the so-called boxing-glove hands.[1] Inflammatory markers may be elevated, but RF and aCCP are negative. In addition patients with RS3PE usually have a dramatic response to low-dose of corticosteroid therapy.[14]

RS3PE is associated to a wide spectrum of clinical associations that makes differential diagnosis challenging.

RS3PE may present as a paraneoplastic syndrome of various malignancies. To our knowledge, there are no specific guidelines for the assessment of possible neoplasms. We referred to the clinical practice guidelines of polymyalgia rheumatica by the Italian Society of Rheumatology, as a reference model.[15]

MSUS demonstrated to be accurate in identifying specific lesions of many rheumatic disorders that may correctly drive the diagnostic process. Erosions at the II MCP or V MTP joints have proven to be specific for RA,[16] while in case of psoriatic arthritis the presence of enthesitis and peritendonitis of the extensor tendon at the MCP level can reveal the disease.[12] In crystal deposition diseases, US is able to detect accurately and reliably both calcium pyrophosphate crystal deposition[9,17] and urate crystals in the joints[10] allowing a correct and even early diagnosis, even before symptoms occurrence. US is also cheap, harmless, feasible. Finally, this scanning technique has been adequately standardized by the EULAR working group on US,[8] reducing operator-dependent variability of findings, thus making US a reliable exam and the best ally in the diagnostic process.

In this case, the multi-site screening of the patient allowed us to exclude any comorbidities and reach the correct diagnosis as demonstrated by the optimal response to therapy. Pain in the shoulders and hips could mimic PMR. However, US demonstrated no inflammatory changes in shoulders and hips, but only degenerative disorders that could explain symptoms. There were no specific lesions for RA or PsA in the hands, while the examination of the fibrocartilage and hyaline cartilage of knees, wrists and I MTP joint excluded the presence of crystal deposition. The whole US examination in these specific sites lasted approximately 12 minutes.

Cantini *et al*. in 1999[18] were the first to use advanced imaging techniques in RS3PE and performed non-enhanced MRI of hands (5 patients) and feet (2 patients) compared to 5 healthy controls. Extensor tendon tenosynovitis was present in 3 patients and flexor tendon tenosynovitis in one. Joint inflammation was detected in 2 patients. Peroneal tendon tenosynovitis was the most frequent finding (2/2) in feet, while one patient also presented with tenosynovitis of the tibialis posterior, flexor digitorum longus and flexor hallucis longus tendon. Joint involvement was present in one patient. However, the number of patients included in the imaging assessment in this study was too low, unilateral and the MRI was carried out without gadolinium. Due to these limitations, it is not possible to draw firm conclusions on the kind of inflammatory involvement in the hands of patients with RS3PE, but, as the authors themselves admitted, the clinical examination was really difficult due to the amount of edema and imaging helped them to address joint involvement in these patients.

In 2005 Klauser *et al*.[19] described the US findings in the hands of patients with RS3PE. The main findings in a series of eight patients were the presence of subcutaneous tissue oedema, joint inflammation and tenosynovitis. In the power Doppler examination, increased vascularity was seen in the subcutaneous tissues in 5/16 hands, in the tendon sheath in 15/48 tendons examined and in 9/96 joints. Contrast enhanced PDUS revealed the presence of vascularity in a statistically significant higher percentage of patients. MRI revealed similar changes in the soft tissues and did not demonstrate any additional benefit over US.

In the same year, Agarwal *et al*.[20] reported similar findings in a series of 10 patients with RS3PE. They also found a prevalent inflammatory involvement of the flexor and extensor tendons of the wrists and hands, but they did not report any findings in the joints.

A recent study by Kawashiri *et al*.[21] tried to assess the differences in US findings between patients with RS3PE and patients with elderly onset rheumatoid arthritis (EORA). Even though the number of patients was small (7 with RS3PE and 22 with EORA), they found significant differences between the patients in the quality of joint inflammation. Patients with EORA mainly had synovial proliferation, while patients with RS3PE presented effusion. Furthermore, flexor tendon tenosynovitis was more severe in patients with RS3PE. Erosions were also found in some patients with EORA, but not in patients with RS3PE. A curious finding is the frequent presence of peritendonitis of the extensor tendon in the MCP joints of patients with RS3PE. This finding is considered to be specific of psoriatic arthritis[22] and the high prevalence of peritendonitis

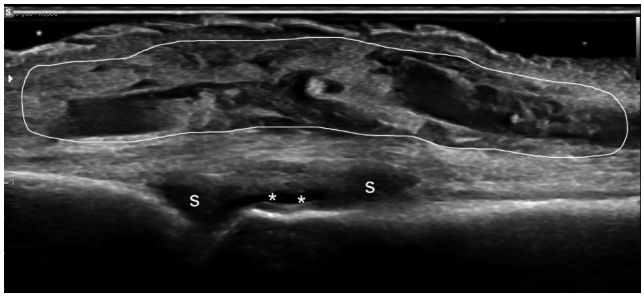

Figure 2. Ultrasound of IV metacarpal-phalangeal joint showing a severe edema of the subcutaneous tissue with synovitis. S, synovits; *, effusion.

Table 1. Laboratory values.

Laboratory test	Initial visit	Normal values
WBC count, $\times 10^9$/L	4.2	4.0-10.0
Hemoglobin, gm/dL	11.9	11-15.7
Platelets $\times 10^9$/L	270	150-400
ESR, mm/hour	85	0-20
CRP level, mg/dL	20	<5
AST, unit/L	18	10-45
ALT, unit/L	22	7-45
LDH, unit/L	140	80-190
Creatinine, mg/dL	0.8	0.8-1.2
Ferritine, ng/mL	500	25-350
TSH, mIU/L	1.45	0.4-4
CPK, U/L	70	30-150
Rheumatoid factor	Negative	<20
aCCP	Negative	<14
ANA	Negative	<1:40
Hepatitis C antibody	Negative	Negative
Hepatitis B surface antigen	Negative	Negative
Hepatitis B core antigen	Negative	Negative

WBC, white blood cells; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; TSH, thyroid-stimulating hormone; CPK, creatine phosphokinase; ANA, anti-nuclear antibodies.

together with the higher prevalence of flexor tenosynovitis could suggest some common mechanisms in the inflammation process in both disorders.

In our case, extensor tendon tenosynovitis was not observed in US, while all other typical imaging features of the disease (subcutaneous oedema, joint inflammation, flexor tenosynovitis) were present. The short duration of the disease (only few days from onset of symptoms to the US exam) may explain partially the incomplete spectrum of inflammatory involvement. However, in our opinion, the main usefulness of US is the ability to perform multisite scanning to rule out or identify other concomitant musculoskeletal diseases that may mimic or be associated to RS3PE. By examining the involved sites only, precious information may be missed and the diagnosis may be misguided. It would be useful to compare ultrasound findings with other imaging investigations, but unfortunately, we did not have other radiological assessments available.

Conclusions

RS3PE is not a frequent entity and could be challenging for the rheumatologist, as it may hide other underlying diseases. Since clinical examination can be compromised by the soft tissues edema, US can be a useful tool to reveal inflammation in the involved sites and make a differential diagnosis easier by highlighting elementary lesions specific of other rheumatologic conditions that may be associated with RS3PE. Until now, no specific US items have been identified for RS3PE, but the number of studies and patients examined is rather low. Imaging studies in large series of patients may help a better identification of the typical manifestations of the disease and provide insights in disease pathogenesis, evolution and outcomes.

References

1. McCarty DJ, O'Duffy JD, Pearson L, et al. Remitting seronegative symmetrical synovitis with pitting edema: RS3PE syndrome. JAMA 1985;254:2763-7.
2. Manger B, Schett G. Paraneoplastic syndromes in rheumatology. Nat Rev Rheumatol 2014;10:662-70.
3. Mainali NR, Schmidt TR, Alweis R, et al. Novel development of remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome due to insulin therapy. Am J Case Rep 2014;15:119-22.
4. Yao Q, Su X, Altman RD. Is remitting seronegative symmetrical synovitis with pitting edema (RS3PE) a subset of rheumatoid arthritis? Semin Arthritis Rheum 2010;40:89-94.
5. Kenzaka T. The Relationship between remitting seronegative symmetrical synovitis with pitting edema and vascular endothelial growth factor and matrix metalloproteinase 3. Intern Med Tokyo Jpn 2020;59:1021-2.
6. Arima K, Origuchi T, Tamai M, et al. RS3PE syndrome presenting as vascular endothelial growth factor associated disorder. Ann Rheum Dis 2005;64:1653-5.
7. Joseph AD, Kumanan T, Aravinthan N, et al. An unusual case of remitting seronegative symmetrical synovitis with pitting edema: case report and literature review. SAGE Open Med Case Rep 2020;8:2050313X20910920.
8. Möller I, Janta I, Backhaus M, et al. The 2017 EULAR standardised procedures for ultrasound imaging in rheumatology. Ann Rheum Dis 2017;annrheumdis-2017-211585.
9. Filippou G, Scanu A, Adinolfi A, et al. Criterion validity of ultrasound in the identification of calcium pyrophosphate crystal deposits at the knee: an OMERACT ultrasound study. Ann Rheum Dis 2020;annrheumdis-2020-217998.
10. Christiansen SN, Østergaard M, Terslev L. Ultrasonography in gout: utility in diagnosis and monitoring. Clin Exp Rheumatol 2018;7.
11. Filippou G, Filippucci E, Mandl P, et al. A critical review of the available evidence on the diagnosis and clinical features of CPPD: do we really need imaging? Clin Rheumatol 2020 [Epub ahead of print].
12. Sakellariou G, Scirè CA, Adinolfi A, et al. Differential diagnosis of inflammatory arthropathies by musculoskeletal ultrasonography: a systematic literature review. Front Med 2020;7:141.
13. D'Agostino M-A, Terslev L, Aegerter P, et al. Scoring ultrasound synovitis in rheumatoid arthritis: A EULAR-OMERACT ultrasound taskforce - Part 1: Definition and development of a standardised, consensus-based scoring system. RMD Open 2017;3.
14. Origuchi T, Arima K, Umeda M, et al. Clinical outcomes in the first year of remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome. Mod Rheumatol 2017;27:150-4.
15. Ughi N, Sebastiani GD, Gerli R, et al. The Italian Society of Rheumatology clinical practice guidelines for the management of polymyalgia rheumatica. Reumatismo 2020;72:1-15.
16. Zayat AS, Ellegaard K, Conaghan PG, et al. The specificity of ultrasound-detected bone erosions for rheumatoid arthritis. Ann Rheum Dis 2015;74:897-903.
17. Filippou G, Scirè CA, Adinolfi A, et al. Identification of calcium pyrophosphate deposition disease (CPPD) by ultrasound: reliability of the OMERACT definitions in an extended set of joints - an international multiobserver study by the OMERACT calcium pyrophosphate deposition disease ultrasound subtask force. Ann Rheum Dis 2018;annrheumdis-2017-212542.
18. Cantini F, Salvarani C, Olivieri I, et al. Remitting seronegative symmetrical synovitis with pitting oedema (RS3PE) syndrome: a prospective follow up and magnetic resonance imaging study. Ann Rheum Dis 1999;58:230-6.
19. Klauser A, Frauscher F, Halpern EJ, et al. Remitting seronegative symmetrical synovitis with pitting edema of the hands: ultrasound, color doppler ultrasound, and magnetic resonance imaging findings. Arthritis Rheum 2005;53:226-33.
20. Agarwal V, Dabra AK, Kaur R, et al. Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome: ultrasonography as a diagnostic tool. Clin Rheumatol 2005;24:476-9.
21. Kawashiri S, Suzuki T, Okada A, et al. Differences in musculoskeletal ultrasound findings between RS3PE syndrome and elderly-onset rheumatoid arthritis. Clin Rheumatol 2020;39:1981-8.
22. Gutierrez M., Draghessi A., Bertolazzi C., et al. Ultrasound in psoriatic arthritis. Can it facilitate a best routine practice in the diagnosis and management of psoriatic arthritis? Clin Rheumatol 2015;34:1847-55.

Non-commercial use only

OPEN ACCESS