

Remitting seronegative symmetrical synovitis with pitting edema (RS3PE): A case report and brief review

Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) is a rare form of inflammatory arthritis, most often affecting elderly individuals and characterized by polyarthritis most commonly affecting the hands and feet in a symmetric fashion, associated with pitting edema on the dorsum of the hands (and occasionally the feet). Symptoms often spontaneously remit and are usually very responsive to low dose glucocorticoids. RS3PE has been considered as forme fruste of polymyalgia rheumatica. It can also occur as a paraneoplastic syndrome and can sometimes be a harbinger of malignancy. This article describes a case of RS3PE, followed by a review of literature about this very intriguing rheumatologic disease.

Rajandeep Paik^{*1,2}

¹Lecturer in Medicine, Harvard Medical School, Massachusetts, USA

²Cambridge Health Alliance, USA

*Author for correspondence:

dr.rajandeep.singh@hotmail.com

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Introduction

Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) is a rare form of inflammatory arthritis, typically affecting elderly men with a clinical picture of symmetric polyarthritis and pitting edema on the dorsum of hands, and sometimes the feet. The pathophysiology of RS3PE is not clearly understood. Several reports have considered this to be a form of polymyalgia rheumatica and even seronegative rheumatoid arthritis, but several differences in the clinical presentation and pathophysiologic mechanisms indicate that it may be a separate entity. Once a diagnosis of RS3PE is made, it should prompt consideration of evaluation for underlying malignancy, as it can often present in the form of a paraneoplastic syndrome. This article presents a case of RS3PE followed by a brief review of literature.

Case presentation

An 85-year-old gentleman with a past medical history significant for hypertension, gout, hyperlipidemia, right femur fracture treated with internal fixation and bladder cancer treated with resection and intravesicular Bacillus Calmette-Guerin, presented with a 3-month history of sudden onset and slowly worsening pain and swelling in his hands, along with milder pain and stiffness in his shoulders, hips and thighs. Additionally, he noted generalized myalgia and overall stiffness in the morning. Prior to the

onset of these symptoms, he led an active lifestyle including frequent kayaking and bicycling, and regular exercise at the gym. At presentation, he reported difficulty with daily tasks like gripping objects and opening doorknobs.

On examination, he had swelling restricted to the dorsum of both hands with pitting edema, without any signs of synovitis. He had mild restriction on internal rotation in his right shoulder associated with pain, but otherwise had no significant difficulty with shoulder or hip movements. The remainder of his exam was fairly unremarkable.

Laboratory testing revealed negative Rheumatoid Factor (RF), anti-Cyclic Citrullinated Peptide (anti-CCP) and Anti-Nuclear Antibody (ANA), normal Thyroid-Stimulating Hormone (TSH), mild anemia with hemoglobin of 11.8 g/dL, elevated erythrocyte sedimentation rate (ESR) 69 mm/hr and elevated ZC-Reactive Protein (CRP) 5.5 mg/dL. Plain radiographs of both hands showed soft tissue swelling, changes consistent with osteoarthritis and no erosions. The overall presentation raised concern of RS3PE. Treatment with prednisone 15 mg daily was instituted.

At a follow up visit one week later, dramatic improvement of all his symptoms was noted. The swelling on the dorsum of his hands had completely resolved. The ESR and CRP returned to normal. At a 4 week follow up visit,

he remained asymptomatic, the anemia had resolved and ESR and CRP remained normal. At this point, tapering of prednisone dose was started. Comprehensive search for underlying malignancy was negative, including CA 19-9, carcinoembryonic antigen, prostate specific antigen, serum and urine protein electrophoresis and computed tomography scans of his chest, abdomen and pelvis. His previously treated bladder cancer was followed by his urologist and cystoscopy was normal.

Discussion

Remitting seronegative symmetrical synovitis with pitting edema is a rare autoimmune condition. The first description was in 1985 in a series of 10 patients by McCarthy et al. when it was believed to be a subset of seronegative rheumatoid arthritis [1].

Over time, several studies have demonstrated a male preponderance and age of onset commonly 70 years or older [2]. Bilateral and symmetric hand involvement is the most common presentation, although occasionally symptoms can be asymmetric or unilateral, and other joints including feet, ankles and shoulders can be involved. Constitutional symptoms including fever, malaise, fatigue and weight loss can be seen. Although the name includes the term synovitis, the most characteristic finding is tenosynovitis of the extensor tendons of the hands, RS3PE has been described in association with other rheumatologic disease including sarcoidosis [3], gout [4], Sjogren syndrome [5] and polymyalgia rheumatica [6,7].

RS3PE has also been observed in the form of a paraneoplastic syndrome in association with solid organ malignancies, and rarely, hematological malignancies [8]. It may occasionally be the harbinger of an underlying malignancy.

It has been postulated that RS3PE may be a subset of Rheumatoid Arthritis (RA), but is now felt to be an entity distinct from RA, based on lack of erosion, seronegativity, excellent prognosis without the use of Disease Modifying Anti-Rheumatic Drugs (DMARDs) and absence of the Human Leukocyte Antigen (HLA) DRB1 genotype [9].

Similarly, RS3PE has been considered by some authors to be a *forme fruste* of polymyalgia rheumatica (PMR), based on several similarities including older age of onset, elevated acute phase reactants and excellent response to glucocorticoids [10,11]. However, there

are some distinctive features including male preponderance, involvement predominantly of distal extremities, shorter duration of disease and significantly lower rates of recurrence. Based on these, RS3PE indeed appears to be an entity separate from PMR.

Acute phase reactants including ESR and CRP are elevated in the majority of patients. RF and anti-CCP are negative by definition. Some cases have noted positive ANA in low titers. Anemia and thrombocytosis can be observed, as in any inflammatory condition. Prior studies looked at elevation of serum Vascular Endothelial Growth Factor (VEGF) and this may be associated with the pathogenesis of RS3PE and may have a future role in diagnosis and management [12].

However, a recent multicenter study found that VEGF level increase in general in rheumatic diseases and this was not associated with specific rheumatic diseases [13]. Plain radiographs do not show erosive disease. Modalities like ultrasound and Magnetic Resonance Imaging (MRI) often shows tenosynovitis in extensor tendons [14].

The authors of a systematic review and meta-analysis in 2016 proposed the following criteria for diagnosis:

- Abrupt onset
- Marked pitting edema of hands (and/or feet)
- Age of onset \geq 60 years
- Good response to short course of medium dose steroids (10-20 mg)
- Absence of radiographic joint erosions [2].

Conclusion

Most patients respond very well to low to moderate doses of glucocorticoids. In terms of tapering, an approach similar to that in PMR can be followed, with beginning of taper in 4-6 weeks after control of symptoms and normalization of acute phase reactants. The presence of malignancy at the time of diagnosis and solid organ tumors were associated with a higher incidence of recurrence after treatment. Symptoms of paraneoplastic RS3PE have been shown to disappear after successful treatment of underlying malignancy.

The decision to perform extensive screening for underlying malignancy should be individualized, based on presence/absence of signs or symptoms of malignancy, cost-effectiveness, unusual features like lack of response to low-medium dose glucocorticoids and history of prior malignancy.

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