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Novel Development of Remitting Seronegative Symmetrical Synovitis with Pitting Edema (RS3PE) Syndrome due to Insulin Therapy

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Male, 67
Final Diagnosis: Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome
Symptoms: Bilateral wrist swelling
Medication: —
Clinical Procedure: —
Specialty: Rheumatology

Objective: Unusual or unexpected effect of treatment

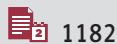
Background: Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome is a rare clinical entity characterized by the sudden onset of inflammatory arthritis and marked pitting edema on upper and lower extremities. RS3PE is considered a rheumatic process distinct from rheumatoid arthritis, which may occasionally represent a paraneoplastic syndrome.

Case Report: Herein, we describe a rare case of RS3PE associated with insulin therapy in a patient with no evidence of underlying malignancy.

Conclusions: To the best of our knowledge, this is the first case report of RS3PE associated with insulin therapy. Physicians should look at the introduction of drugs as possible triggers for the development of RS3PE.

MeSH Keywords: Steroid • RS3PE • Synovitis • Insulin – therapeutic use • Hydroxychloroquine

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Background

Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome, first described in 1985 by McCarty et al. [1], is characterized by the sudden onset of inflammatory arthritis, as well as pitting edema over the affected joints. RS3PE most commonly occurs in elderly men. Its association with late-onset rheumatoid arthritis and polymyalgia rheumatica has been debated [1–4]. The disease usually has a benign course, but may represent a paraneoplastic syndrome [2,5,6]. We present what we believe to be the first case report of RS3PE syndrome associated with the introduction of insulin therapy.

Case Report

A 67-year-old man with a history of well-controlled type II diabetes mellitus (HA1C=6.6%), essential hypertension, and hyperlipidemia without end-organ sequelae presented with acutely worsening bilateral, swollen, painful large joints and significant bilateral hand edema after a 5-month history of waxing and waning diffuse arthralgias, bilateral hand and wrist swelling, and generalized stiffness. The pattern of symptoms began within several days of initiating various forms of insulin (Table 1), leading to their successive discontinuation and initiation of a different form of insulin. Within 24 hours of initiation of multiple forms of insulin, he experienced marked increase in stiffness, hand swelling, and limitation of basic activities of daily living. In his own words, some of his remarkable complaints were: “hands so swollen they were unusable,” “unable to comb my hair due to pain and stiffness,” “so sore and stiff when I wake up, it takes me hours to get out of bed,” and “unable to get out of tub I climbed in and my wife had to help me out of it.” At the time of presentation, his other medications were metformin, ramipril, and aliskiren. His HMG CoA reductase inhibitor had already been discontinued 3 weeks prior to his most recent and most acute presentation, with no change in symptomatology. He did not have any history of drug allergy or systemic rheumatic illness.

Physical examination revealed tenosynovitis characterized by swelling and moderate tenderness of the metacarpophalangeal and proximal interphalangeal joints bilaterally. There was marked non-tender pitting edema on the dorsum of both hands and wrist joints associated with reduced range of motion and reduced grip strength. Bilateral ankles were also remarkably swollen. There was no jugular venous distension, hepatojugular reflux, rales, or stigmata of chronic liver disease. Physical exam results were otherwise normal.

Laboratory evaluation revealed normal erythrocyte sedimentation rate (ESR), creatine kinase (CK), and aldolase, with negative antinuclear antibody (ANA), anti-neutrophil cytoplasmic antibody (ANCA), rheumatoid factor (RF), anti-cyclic citrullinated peptide (ACPA), and anti-insulin antibody. Hand and foot X-rays revealed only soft-tissue swelling without evidence of joint destruction.

Due to the absence of complete remission with removal of insulin during the fourth episode, a diagnosis of inflammatory arthritis was considered, and the patient was placed on prednisone 20 mg daily. Within 48 hours, he reported resolution of all symptoms. With tapering of prednisone, symptoms recurred, necessitating addition of hydroxychloroquine because his blood sugars became uncontrolled on the higher dosages of prednisone necessary to keep his symptoms controlled. His age-appropriate cancer screening results were all negative. Given the presentation of waxing and waning symmetric polyarthralgia without serologic findings and the presence of pitting hand and feet edema with dramatic response to prednisone, a diagnosis of RS3PE was made. His diabetes has since been managed with metformin and sitagliptin.

Discussion

RS3PE syndrome is such a rare clinical entity that the actual incidence of the disease is unknown. Patients with RS3PE typically present with sudden onset of polyarthritis, with marked pitting edema, and reduced grip strength and range of motion.

Table 1. Insulin timeline.

Insulin type	Insulin start date	Symptom onset*	Insulin stop date	Symptom resolution
Lantus/NovoLog	1/11/11	1/15/11	3/22/11	3/24/11
Lantus (increased)	5/09/11	5/12/11	7/1/11	7/3/11
Levemir	7/13/11	7/14/11	7/29/11	8/1/11
Humulin (70/30)	8/2/11	8/3/11	8/8/11	9/4/11 after starting prednisone from 9/2/11

* Symptoms – pain, swelling, and stiffness of the affected joints (mainly hands and feet).

ESR is usually, but not always, elevated, with negative ANA, ANCA, RF, and ACPA [7]. X-rays of the affected joints reveal soft-tissue swelling and no evidence of joint destruction. RS3PE usually responds very well to low-dose corticosteroid or hydroxychloroquine unless associated with malignancy [6,7].

Although previously described in the literature on associations of RS3PE with multiple rheumatologic diseases, Yao et al. [8] described RS3PE as a distinct entity based on clinical, laboratory findings, and genetic differences. There are also multiple cases in which the arthropathy has been the sentinel event in detection of both solid and liquid malignancy, with as many as 54% of patients eventually developing cancer in the largest case series, and several smaller series indicating cancer diagnoses being made up to 15 years after the diagnosis of RS3PE [5,8–10]. More severe disease with systemic symptoms and poor response to therapy increase the probability that this presentation represents a paraneoplastic process; thus, age-appropriate cancer screening is recommended [8,9]. Negative results of age-appropriate cancer screenings, dramatic response to steroids, and lack of recurrence led us to believe that this case was not paraneoplasia.

Although there are cases associated with infections, no single precipitating infectious agent has ever been identified [11]. There does not appear to be an association between rheumatoid arthritis and RS3PE, as was originally hypothesized [8]. RS3PE has not been clearly linked with HLA-DR antigens, thus distinguishing itself from rheumatoid arthritis (RA) and polymyalgia rheumatic (PMR) association [12]. RS3PE has been suggested to be associated with many disease conditions and drugs. For example, Yamauchi et al. described 2 cases of RS3PE associated with treatment with a dipeptidyl peptidase-4 (DPP4) inhibitor [13]. However, our patient was not on a DPP4 inhibitor until after the fourth episode. While the exact mechanism is still unknown, elevated vascular endothelial growth factor (VEGF) activity has been described as a key factor in the pathogenesis of RS3PE [14]. VEGF is a potent angiogenic and vasogenic molecule, perhaps due to synovial hypervascularity and subcutaneous edema, respectively [14–16]. Insulin directly increases VEGF-A mRNA

and protein expression in various tissues, including cardiac myocytes and renal podocytes [17,18]. We hypothesize that elevated VEGF level secondary to insulin in a predisposed individual may trigger RS3PE, as in our case. However, due to the lack of availability of VEGF assays in our lab during the initial evaluation, we cannot demonstrate this conclusively in our patient.

Despite this, the temporal sequence of events suggests that the insulin therapy contributed to acute worsening of symptoms of RS3PE in our case (Table 1). Symptoms flared and resolved rapidly with the introduction and withdrawal of each new insulin preparation until the fourth episode. Multiple formulations from different manufacturers were used. Ingredient lists from each preparation were reviewed, but other than the insulin, there was no common ingredient for which it was safe to perform a challenge test. Over the last 2 years, the patient has continued on DPP4 inhibitor and metformin therapy without recurrence of symptoms, and in the last 6 months he has successfully been weaned off of hydroxychloroquine.

Conclusions

To the best of our knowledge, this is the first case report of RS3PE associated with insulin therapy. Physicians should regard the introduction of drugs as possible triggers for the development of RS3PE. Further study is required to define the exact pathophysiology of the syndrome.

Acknowledgement

We deeply acknowledge our patient for the consent to publish this case report for teaching medical professionals to better help their patients.

Competing interests

The authors have no competing interest and no financial disclosure to make.

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