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DAVETLİ DERLEME/INVITED REVIEW

Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome

Tekrarlayıcı seronegatif pitting ödemli simetrik sinovit (RS3PE) sendromu

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Abstract
Remitting seronegative symmetrical synovitis with pitting edema is a rare rheumatological disorder that presents with symmetrical hand and/or foot edema resembling rheumatoid arthritis. It is generally seen in male patients in older age, but atypical cases in different age groups have been documented. Although no clear mechanism has been described, certain genetic and environmental factors have been suggested for etiopathogenesis. Medical treatment is mainly focused on glucocorticoid therapy. This article aims to discuss the Remitting seronegative symmetrical synovitis with pitting edema syndrome and to review the current literature.
Key words: Remitting seronegative symmetrical synovitis with pitting edema, RS3PE, hand edema, tenosynovitis, rheumatoid arthritis.

Öz
Tekrarlayıcı seronegatif pitting ödemli simetrik sinovit sendromu, romatoid artriti andıran simetrik el ve/veya ayak ödemi ile prezente olan nadir görülen bir hastalıktır. Genellikle ileri yaş erkek hastalarda görülür fakat farklı yaş gruplarında görülen atipik vakalar da bulunmaktadır. Net bir mekanizma tanımlanmamış olmasına rağmen, etiyopatogenezde belli genetik ve çevresel faktörler öne sürülmektedir. Tedavi, esasen glukokortikoid tedavisi üzerine odaklanmaktadır. Bu derlemede Tekrarlayıcı seronegatif pitting ödemli simetrik sinovit sendromunun tartışılması ve literatürün gözden geçirilmesi amaçlanmıştır.

Anahtar kelimeler: Tekrarlayıcı seronegatif pitting ödemli simetrik sinovit, RS3PE, el ödemi, tenosinovit, romatoid artrit.

INTRODUCTION

Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) is a rare clinical condition which was first described by McCarty et al in 1985[1]. It is characterized by acute onset symmetrical polyarthritis/polysynovitis of the hands and feet resembling rheumatoid arthritis (RA), but also with pitting edema, distal tenosynovitis, dramatic response to low dose glucocorticoids and lack of joint erosions[2,3]. McCarty et al. first reported the entity which was a distinct form of seronegative rheumatoid arthritis like polyarthritis and polymyalgia rheumatica (PMR)[4]. In their first report, the authors presented 10 elderly patients (8 men and 2 women) who had symmetrical polysynovitis of acute onset with pitting edema and named the entity "remitting seronegative symmetrical synovitis with pitting edema"[5].

There is still an ongoing debate whether RS3PE is a variant form of RA or a distinct entity. Some believe that patients with RS3PE represented a subset of RA. For example, Bhakta and Pease classified the patients who fulfilled the RS3PE criteria into the Late-onset rheumatoid arthritis (LORA) group[6]. However, Schaeverbeke et al. suggested that RS3PE is a discrete syndrome[7]. Although it has similarities with LORA, young-onset rheumatoid arthritis (YORA), and PMR, some clinical features including characteristic pitting edema, negative rheumatoid

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factor (RF), lack of subcutaneous nodules, absence of radiographic erosions, no association with HLA DRB1 alleles and good response to glucocorticoids are distinctive for RS3PE[8].

This article aims to discuss the etiopathogenesis, clinical, laboratory, imaging features and treatment approaches of RS3PE syndrome and to review the current literature.

ETIOPATHOGENESIS

RS3PE commonly affects men in older age and has a variable male/female ratio ranging from 2/1 to 5/1[4,5]. Though it is a rare clinical disorder, there is no enough data regarding the prevalence and incidence rates of the entity. In a study by Okumura et al., prevalence of RS3PE has been reported as 0,09% in Japanese population over the age of 50[9]. To date, a number of case reports and series have been presented in international literature[10,11].

The etiology of RS3PE is unknown. There are a number of studies about RS3PE that support the disorder with potentially heterogeneous etiologies[12]. HLA serotypes, infectious agents or environmental factors might be associated with the disorder. It was initially reported to be associated with HLA B7 and this HLA antigen has been reported in 59% of the patients. HLA A2 association with RS3PE has also been reported[8,13]. HLA CW7 and HLA DQW2 tissue antigens have been found in some cases[11]. Vascular endothelial growth factor (VEGF) is an important factor which precipitates angiogenesis and, as a result of high serum level of VEGF, is triggered to vasodilation and increased vascular permeability[12,14]. Various reports have established the role of VEGF as a major contributor to polysynovitis and subcutaneous edema by increasing the vascular permeability. Elevated VEGF levels have been reported as decreased after glucocorticoid treatment. This condition supports the assertion that reduced VEGF levels are associated with improvement of the syndrome. Aritma et al., have suggested that prednisolone treatment causes a reduction of VEGF levels in patients with RS3PE syndrome[14]. In contrast to RA, elevated VEGF plays an important role in the pathogenesis and it might be helpful to measure the serum VEGF levels for the diagnosis of RS3PE[8]. IL-6 has been found to be elevated in the synovial fluid of patients with RS3PE[11,15]. Furthermore, VEGF levels, which suspected to trigger pitting edema, were found to be higher in a patient with sarcoidosis who had edema of the extremities resembling RS3PE[15]. In addition, increased matrix metalloproteinase 3 (MMP-3) levels especially have been associated with paraneoplastic RS3PE syndrome. The authors concluded that high MMP-3 level is a meaningful marker of RS3PE syndrome associated with malignancy and helps to diagnose earlier[16].

Some infectious agents have also been linked to RS3PE. Michaels and Hochmann presented a case of RS3PE with an accompanying campylobacter jejuni infection[17,18]. HCV associated cryoglobulinemia[19] and leprosy[20] may be associated with RS3PE. Mycoplasma pneumoniae has been suggested as a causative agent for RS3PE[21]. Russell et al. failed to demonstrate the association of HTLV antigens with RS3PE syndrome[22]. In another case report possible association between streptobacillus moniliformis and RS3PE has been recognized[23]. Perandones et al. presented a 36-year-old woman admitted with RS3PE syndrome, and the authors found Parvovirus B19 seropositivity and followed-up with the patient for 9 years. No other cause for RS3PE has been found and the authors suggested an etiological relationship between RS3PE and Parvovirus B19 infection[24]. Similarly, Drago et al. described another two cases who had RS3PE syndrome associated with Parvovirus B19 infection[25]. In general no clear association was reported between an infectious agent and RS3PE.

CLINICAL CHARACTERISTICS

The main clinical manifestations of RS3PE are described as symmetrical polysynovitis of sudden onset. Pitting edema of the dorsum of both hands and feet is associated with flexor and extensor tenosynovitis, which sometimes coexists with large joint arthritis. Flexion contractures of fingers and wrist may be seen due to tenosynovitis or occasionally arthritis. McCarty et al., described predominant involvement of the flexor tendons of the hands, while other authors have reported both flexor and extensor tenosynovitis[1,20,26,27]. Formerly, because of the symmetrical synovitis involving predominantly wrists, carpal joints, small joints of hand as well as the involvement of flexor tendon sheaths which accompanied by a marked dorsal swelling of the hands, it was thought that flexor tenosynovitis, abnormal permeability of the capillary network as a result of inflammatory process that played an important role in the pathogenesis of the

edema[1,13,17,28]. The edema is especially common in both of the upper extremities, but unilateral hand involvement (figure 1) or involvement of the lower extremities have been reported as well. There have been several cases of asymmetrical synovitis and pitting edema in literature[3,17,29]. Keenan et al. presented 6 cases with unilateral RS3PE. According to the review, most of the cases had a neurologic deficit such as cerebrovascular accident and Erb's palsy[30]. Özşahin et al., published a case of unilateral RS3PE with a previous diagnosis of RA. The presented patient with RS3PE had discontinued the diseases-modifying antirheumatic drug (DMARD) therapy for 3 years[29]. In contrast, Varshney et al. presented a case of seronegative RA with unilateral RS3PE who had been under the treatment of DMARD therapy[3].

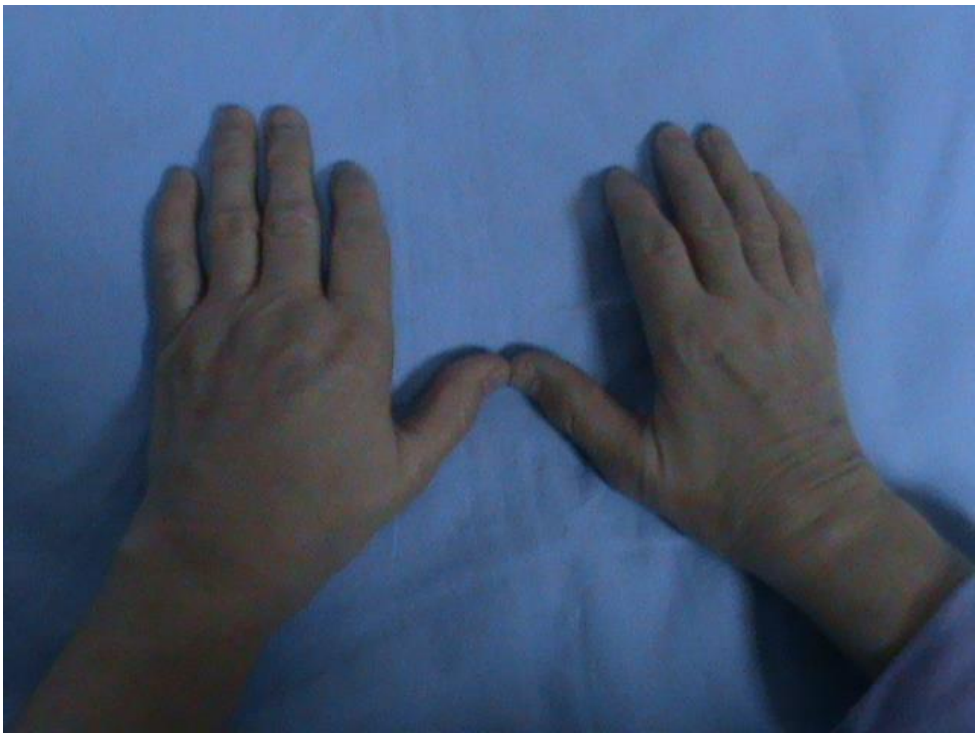

Figure 1. Unilateral hand edema of the patient with RS3PE syndrome

ASSOCIATED CONDITIONS

The majority of cases involving RS3PE are idiopathic[30]. However, rheumatic diseases, both malign and benign tumors and drugs have been associated with RS3PE syndrome[12]. Most common malignancies reported were non-Hodgkin's lymphoma, leukemia, myelodysplastic syndrome and solid tumors including prostate, lung, breast, bladder, ovary, endometrium and gastrointestinal malignancies[4,12]. Yao et al. researched the literature of RS3PE and suggested that malignancy rate associated with RS3PE might be as high as 54%[8]. But in a newer report, malignancy rate based upon the data of different studies on RS3PE patients has been estimated to be 31%[12]. Cases of RS3PE syndrome with underlying malignancy generally have systematic manifestations such as fever, anorexia and weight loss, as well as poor response to corticosteroids[31,32]. Accordingly, patients with diagnosis of RS3PE without malignancy must be followed for hematological or solid malignancies which can be diagnosed during follow-up[4,33]. Therefore, patients presenting with RS3PE syndrome must be carefully examined especially in atypical cases such as unilateral involvement or patients at younger ages. Rheumatic diseases include systemic lupus erythematosus, Sjögren's syndrome,

scleroderma, spondyloarthropathies, gout, amyloidosis, relapsing polychondritis, sarcoidosis and vasculitis (polyarteritis nodosa, temporal arteritis)[34-39]. Spondyloarthropathies and chondrocalcinosis generally characterized by asymmetric involvement. Otherwise, amyloidal arthropathy can cause pitting edema, but this is progressive and irreversible[40,41]. Rarely, RS3PE might be associated with drugs such as rifampicin, dipeptidyl peptidase-4 inhibitors, insulin and intravesical bacillus Calmette-Guérin (BCG) treatment[12,32,42,43]. Additionally, other conditions such as diabetes mellitus or Kaposi sarcoma may accompany with RS3PE (table 1)[25,44].

Table 1. RS3PE-associated conditions

Solid malignancies	Gastric, hepatocellular, colon, pancreas, prostate and bladder carcinomas, endometrial carcinoma, breast and pulmonary malignancies
Hematological malignancies	Acute leukemia, Hodgkin/Non-Hodgkin lymphoma, myelodysplastic syndrome
Rheumatic diseases	Systemic lupus erythematosus, Sjögren's syndrome, Scleroderma, Spondyloarthropathies, crystal-associated arthritis, sarcoidosis, vasculitis
Infectious agents	Mycobacterium tuberculosis, Mycobacterium pneumonia, Mycobacterium leprae, Streptobacillus moniliformis, Escherichia coli, Campylobacter jejuni, Bacillus Calmette-Guérin
Neurologic disorders	Stroke, Parkinson's disease, Acute intracranial hemorrhage
Drugs	Rifampicin, Dipeptidyl peptidase-4 inhibitors, insulin
Others	Diabetes mellitus, Kaposi sarcoma

DIAGNOSTIC CRITERIA

In 1985, McCarty et al. first described the disorder as a different entity with clinical features of pitting edema of both hands, sudden onset of polyarthritis, older age, rheumatoid factor (RF) seronegativity and absence of radiographic joint erosion[1,8]. After the first description of the syndrome, Olive et al. proposed the following diagnostic criteria in 1997: i) age above 50, ii) negative RF, iii) pitting edema of both hands, iv) acute onset polyarthritis[45,46].

Although, the diagnostic above mentioned criteria are used in the diagnosis, cases also displayed unilateral hand edema, positive anti-CCP and included cases with female gender and younger age. In summary, no unified diagnostic criteria have been established, as many difficulties are encountered while attempting diagnosis[10].

DIFFERENTIAL DIAGNOSIS

Rheumatoid arthritis and polymyalgia rheumatica are the most common rheumatological diseases that interfere with RS3PE. LORA may be confused with the disorder, but patients with RA have bony erosion and positive RF in contrast to RS3PE. PMR involves large joints and is often seen in females. In contrast, small joints are affected without bony erosion and male predominance is seen in patients with RS3PE (Table 2)[40,47,48].

Additionally, hypothyroidism, congestive heart failure, nephrotic syndrome, hepatic diseases, and local factors such as venous insufficiency, lymphedema, cellulitis, osteomyelitis, complex regional pain syndrome, carpal tunnel syndrome, and tenosynovitis should be distinguished[4,41].

LABORATORY AND IMAGING

There is no pathognomonic laboratory test currently used in the diagnosis of RS3PE. Mild to moderate anemia may be present together with the elevated levels of ESR, CRP and fibrinogen[31,49]. RF, ANA and Anti-CCP are generally negative. Positive HLA B7 and HLA A2 have been reported in RS3PE but no association with HLA DRB1 has been described[8,42].

Radiographs of hands and wrists show no evidence of articular erosion. Tenosynovitis of extensor and flexor tendons, which cause edema of the hands and feet, can be shown by magnetic resonance imaging (MRI) and ultrasonographic evaluation (US)[26,31]. McCarty et al. demonstrated flexor tenosynovitis rather than arthritis in patients with RS3PE syndrome[1]. However, Cantini et al. observed both extensor and flexor tenosynovitis, but predominantly extensor tenosynovitis is more likely

to cause swelling and pitting of the hands[27,36]. Additionally, joint synovitis was demonstrated through MRI which is valuable for both diagnosis of the syndrome and following the disease activity in RS3PE[26,31]. US and color doppler ultrasound (CDUS) are useful tools that could demonstrate the synovial proliferation in to the tendon sheaths[50]. Similarly, US is not only a diagnostic tool in the assessment of tenosynovitis in patients with RS3PE, but also helpful in the follow-up of patients[27]. Whole body Ga-67 scan can show elevated uptake in lesions of hands and feet. Imaging modalities are very important tools in diagnosis of the patients with RS3PE[31].

Table 2. Comparison between RS3PE, LORA, YORA and PMR

Clinical features	RS3PE	LORA	YORA	PMR
Onset age (years)	>60	≥65	<65	>60
Sex (Male/Female)	M>F	F≈M	F>M	F>M
Small joint involvement	Mild	Mild-Prominent	Prominent	Mild
Hand deformity	None	Less	Often	None
Pitting edema	Prominent	Unusual	None	None
Pain/Stiffness in pelvic girdle	Less	Rare	Rare	Often
Anti-CCP antibody	None	Frequent	More Frequent	Less
Rheumatoid factor	None	Frequent	Frequent	Less
Association with HLA	HLA-B7, A2	HLA-DRB1, DR4	HLA-DRB1, DR4	HLA-DR4
Radiographic erosion	No	Yes	Yes	No
Synovitis and/or pannus by MRI or ultrasonography	Uncommon-mild synovitis, marked tenosynovitis of both flexor and extensor tendons	Marked	Marked	Uncommon-mild
Response to low dose prednisone (10-15 mg/day)	Dramatic	Usually incomplete	Usually incomplete	Dramatic
Prognosis	Very good	Good	Fair	Good(frequent relapses)
Remission	Yes	Yes,with DMARDs	Yes,with DMARDs (Less than LORA)	Yes (takes 2-3 years)

RS3PE: Remitting seronegative symmetrical synovitis with pitting edema, LORA: Late-onset rheumatoid arthritis, YORA: Young-onset rheumatoid arthritis, PMR: Polymyalgia rheumatica, MRI: Magnetic resonance imaging, DMARD: Diseases-modifying antirheumatic drug.

TREATMENT AND PROGNOSIS

Management of RS3PE syndrome includes a number of medical therapies but the main treatment of the disease is to start the low dose prednisolone medication which also helps to confirm the diagnosis[17]. Patients who had RS3PE syndrome without underlying conditions generally respond well to prednisolone treatment with no recurrence noted in the follow up period. In general, 10-20 mg/day prednisolone treatment has been reported to cause a dramatic response with full remission in 6 to 18 months[8,12,40]. Glucocorticoid therapy provides symptomatic improvement within 24-72 hours. Li et al. suggested using prednisolone or glucocorticoid equivalents 10-15 mg daily for 2 to 3 weeks. The dose may be tapered every week until the lowest dose which can control the disease progression[12]. Finnell et al. applied a medication protocol where low dose prednisone started on 15 mg/day which and was reduced 1 mg/week until patient took 10 mg daily. Thereafter, the prednisone was reduced 1 mg every 2 weeks until the therapy was complete. The researchers continued the treatment 25 weeks and observed improvement of symptoms and manifestations[17]. Glucocorticoid therapy is usually given orally. In contrast, a case who had RS3PE following acute intracranial hemorrhage, administered high dose prednisolone (40 mg, methylprednisolone) intravenously[49]. Furthermore, a patient with RS3PE caused by crystal-induced arthritis of the wrist was successfully treated sequentially by intraarticular corticosteroid injection with nonsteroidal anti-inflammatory drugs (NSAIDs) such as loxoprofen sodium hydrate and diclofenac sodium[35]. Other medical therapies for

RS3PE include DMARDs, aspirin, NSAIDs, diuretics, and gold salt injections[8,10,17,51].

DMARDs therapy, particularly hydroxychloroquine (HCQ) (400 mg/day), might be beneficial and is considered to prevent recurrence in some cases[8,10,19,49]. NSAIDs and HCQ may provide an additional advantage to small doses of prednisolone[11]. The gold salt and methotrexate are both rarely needed and are not widely studied[8,12,51]. Mehta et al. presented a patient who had RS3PE associated with gout and did not respond to glucocorticoids. The patient was successfully treated with etanercept, which enables tumor necrosis factor alpha (TNF-alpha) blockade. The authors suggested that TNF-alpha inhibition therapy may be effective in steroid resistant RS3PE cases after malignancy has been excluded[52]. As the cases associated with neoplasia respond poorly to glucocorticoid therapy, treatment of the underlying malignancy must be the first step[11,12]. Manifestations of RS3PE patients might ameliorate after surgical resection of the tumor or chemotherapy[12,36].

Low degree flexion contractures on wrist and fingers may be permanent. Therefore, early rehabilitation program including range of motion exercises have to be applied simultaneously with medical treatment. Although no specific physical therapy program is reported, range of motion exercises for affected joints, wrist splints and physical modalities may be used in the management of patients with RS3PE[17]. Nevertheless, there is a refractory edema which does not respond to conventional physical therapy, bed rest, elevation and diuretics but improves with glucocorticoid treatment. Therefore, it is essential to use low dose corticosteroid medication in RS3PE syndrome initially.

Prognosis of RS3PE is generally very good with the exception of concomitant neoplasia. There are still unsolved problems to predict which patients will have a benign and self-limiting course and which will have a more progressive disease[12,53].

CONCLUSION

In conclusion, inflammatory swelling with pitting edema of hands and feet may be due to RS3PE syndrome. Although clear diagnostic criteria have been described, it still remains difficult to differentiate the entity from various disorders. In addition, as RS3PE may be associated with rheumatological and malign diseases, it is important to investigate the patients carefully in order to establish a clear diagnosis and treatment.

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