Case Report

Syndrome of Remitting Seronegative Symmetrical Synovitis with Pitting Oedema (RS_3PE)

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Abstract

RS_3PE syndrome, often mimicking rheumatoid arthritis (RA) or polymyalgia rheumatica (PMR), has puzzled the rheumatologists until late'80s. Though the nature of the disease still remains illusive, the outcome is excellent. This present study analyzes the clinical, radiological and immunogenetical characteristics of five patients diagnosed with RS_3PE syndrome, with review of literature. ©

Introduction

RS_3PE syndrome is used to describe patients who have peripheral seronegative, symmetrical polyarthritis associated with tenosynovitis, and pitting oedema present mainly over the dorsum of hands, especially in a man older than 60 years. Whether the RS_3PE is a unique disease or syndrome has long been discussed, the real nature of the syndrome is still a matter of debate. However, it is now considered to be a distinctive entity. The 'definitive diagnostic criteria' of the syndrome includes a subset of seronegative symmetrical polyarthritis of the aged characterized by dramatic onset of pitting oedema of the hands, male predominance, old age, exquisite response to corticosteroids, and long term remission after withdrawal of drugs.[1] Meticulous history taking, careful clinical examination makes the diagnosis easy for an alert clinician. Though the disease is often very painful necessitating hospitalization, the course remains benign without any systemic effect, and shows an excellent response with low dose corticosteroids. This is why, though rare, a treatable condition like RS_3PE syndrome is analyzed here.

Case Reports

Case 1

A male patient aged 68 years, cultivator by occupation, presented in the Rheumatology Clinic of our Institution in the last week of October 2003 with chief complaints of symmetrical polyarthritis involving wrists, elbows, carpal joints, metacarpophalangeal (MCP) and interphalangeal (IP) joints of the hands, and ankle joints associated with inflammation of flexor tendon sheaths of the hands. The onset was dramatically sudden and the patient was in acute agonizing pain with involvement of all the above-mentioned joints within a span of three hours. The hands, especially to speak of the dorsum of the hands, were appeared puffy; there were presence of swelling over dorsum of feet and pretibial areas. No preceding history of trauma, headache, fever, sexual promiscuity, drug intake or diarrhoea was obtained.

Examination revealed acute onset symmetrical polysynovitis of the affected joints associated with involvement of flexor digitorum tendons of the hands. The swollen joints were acutely tender on palpation. Pitting oedema was noted over dorsum of hands as well as feet and pretibial areas. The skin creases over the wrists were obliterated. There was limitation of movements in wrists, fingers and ankles, and the handgrip was weak as well as painful. Actually, he was unable to make a complete fist. The axial skeleton was unaffected. The proximal joints of the limbs were spared. Tenderness over temporal artery, scalp or muscles was not present; temporal artery pulsation was palpable. There was absence of subcutaneous nodules. His vital parameters did not reveal any abnormality. BP was recorded to be 165/85 mm of Hg. Examination of other systems, skin, eyes and ophthalmoscopy were essentially normal. The joints were sufficiently painful and tender, requiring indoor admission.

The investigation profile revealed: Hb 12.8 g/dl, TC 8700/mm^3 with N_{69} L_{26} M_2 E_3, platelets 2 lacs/mm^3, ESR 78 mm in the first hour (Westergren), total protein 6.2 g/dl with albumin 2.7g/dl, rheumatoid factor (RF) – negative, antinuclear factor (ANF) – negative, uric acid 4.8 mg/dl and C-reactive protein (CRP) 12 mg/ml. Blood sugar (F), urea and creatinine levels were respectively 98 mg/dl, 32 mg/dl and 1.2 mg/dl. Microscopic

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examination of urine, thyroid status and chest X-ray were essentially normal. X-ray of the joints did not reveal any erosion. Ultrasonography (USG) diagnosed tenosynovitis on the basis of hypoechoic signal in both transverse and longitudinal planes around the tendon sheaths of the hands. Tenosynovitis of the flexor and extensor tendons at wrist as well as metacarpal heads, and extensor digitorum longus were detected. HLA typing of the patient was positive for B_7.

A provisional diagnosis of RS_3PE syndrome was made, and aspirin (enteric coated, 325 mg, thrice daily after meal with antacid) plus hydroxychloroquine (200 mg, twice daily after meal) were given to the patient. The joint pain started subsiding gradually but oedema persisted. The patient was then put on to prednisolone, 10 mg per day, orally after breakfast. Dramatic relief with low dose prednisolone was noted within 6 weeks of therapy and marked improvement was attained after 7 months so far as joint pain, oedema and grip-strength were concerned. There was no residual disability.

Case 2

A housewife of 73 years presented in June 2004 with abrupt onset of symmetrical arthritis of both MCP and IP joints, which was associated with swelling of back of both the hands. She had added involvement of both shoulders and knee joints. Morning stiffness was profound and persisted for two hours. She was suffering from systemic hypertension for the last 30 years. Examination showed severe pitting oedema of dorsum of both the hands (right>left) with swollen and tender MCP, IP joints of hands, and shoulder and knee joints. Oedema was restricted only to dorsum of the hands and the grip-strength was poor. Mild effusion was present in both the knee joints. Her ESR was 102 mm in the first hour, RF was positive, ANF was negative, and CRP level was 67 mg/ml. The complete blood count, liver, renal and thyroid function tests were essentially normal. Synovial biopsy showed non-specific chronic sinovitis. She had complete remission after 11 months of therapy with 15 mg of prednisolone per day. Clinical response was remarkably rapid without having any residual deformity or debility after remission.

Case 3

A retired male shopkeeper of 77 years presented with an abrupt onset of pain in MCP and IP joints associated with swelling of both the hands in September 1999. He had one and half hours of morning stiffness but no other joint complaints. History regarding constitutional symptoms was absent. Past medical history was unremarkable. Examination revealed pitting oedema of the dorsum of both the hands with swollen and tender MCPs, severe tenosynovitis of the flexor digitorum tendons of hands; wrists were swollen and the grip-strength was poor. Oedema of legs was also present. The axial skeleton and the proximal joints of the limbs were spared. Tenderness over temporal artery was not present. His vital parameters were essentially normal. The ESR was increased at 62 mm in the first hour. The complete blood count, renal, and liver function tests were within normal limits. He showed clinical and electrodiagnostic studies consistent with carpal tunnel syndrome. RF and ANF were negative, and CRP level was normal. The patient was treated with 20 mg of prednisolone per day with a rapid clinical remission. Complete remission came after 16 months of treatment; for the last 10 months, he was on 10 mg prednisolone per day. There was no residual disability and the ESR was normal. Mild relapse occurred at approximately one year after remission but he responded again to low dose of prednisolone. Further follow-up did not reveal any relapse.

Case 4

A 52 years male rickshaw-puller presented in August 2001 with two weeks' history of acutely developing pain in IP joints and MCP joints of the hands, wrists, elbows, shoulders, hips, knees, ankles and metatarsophalangeal joints as well as huge pitting oedema of the dorsum of the hands. Oedema was more pronounced on the left side than on the right side. Morning stiffness persisted for 45 minutes. He was incapacitated with agonizing pain and complained of paraesthesia of the left hand. Examination revealed severe pitting oedema of the left hand with swollen and tender joints on both sides (mentioned above) with acute tenderness in MCP and IP joints. The ESR was 34 mm in the first hour; RF and ANF were negative, and CRP level was 22 mg/ml. His HLA phenotype came out to be B7. Complete remission of his pain and oedema was attained after 9 months of continuous treatment with 15 mg of prednisolone per day. There was no flare up after tapering the dose of corticosteroids. After remission, he did not complain of any residual disability.

Case 5

On September 2000, a retired male school teacher of 81 years presented in our Institution with pneumonia. During the convalescence, he developed symmetrical swelling of hands and feet associated with acutely developing pain in small joints of hands (MCP and IPs) and feet with an added feature of oedema of both the hands. He had half an hour of morning stiffness. He was a patient of type 2 diabetes mellitus with peripheral vascular disease for the last 24 years. Examination demonstrated huge pitting oedema of the dorsum of both the hands, swollen and tender small joints of hands and feet, and tenosinovitis of flexor tendons of hands. Investigations revealed mild anaemia, ESR 52 mm in the first hour, and blood sugar (PP) 220 mg/dl. RF as well as ANF were negative and CRP level was14 mg/ml. The complete blood count, renal and liver function tests did not reveal any abnormality. Considering the age, non-steroidal anti-inflammatory drugs (NSAID) and prednisolone (10 mg per day) were started cautiously

Table 1 : Differential diagnosis of arthritis and oedema of the hands[1]

Diseases	Clinical features	Investigations
RS_3PE syndrome	Aged male. Symmetrical polysinovitis. Dramatic response to low dose corticosteroids. Long term remission after withdrawal. Good prognosis	Negative RF and ANF. Absent bony erosion on X-ray
Mixed connective tissue disease (Sharp syndrome)	Young female. Raynaud's phenomenon +	High titre ANF (speckled) with anti-native ribonucleoprotein
CPPD crystal arthropathy (chondrocalcinosis)	Predominantly elderly female. Absence of constitutional symptoms. Asymmetric oedema. Responsive to NSAIDs	Chondrocalcinosis on hands, knee, pelvis on X-ray. CPPD (calcium pyrophosphate dihydrate) crystal demonstration by polarised light analysis of synovial fluid
Reflex sympathic dystrophy (Sudeck's disease)	Exquisitely painful oedema (often bilateral), vasomotor and skin alterations. True arthritis absent, predisposing factors +	Absent markers of systemic inflammation. Radiology (X-ray, bone scintigram and MRI) helpful
Amyloid arthropathy	Rare disease, firm pseudo-oedema. Frequent carpal tunnel syndrome, nodules +; slow and insidious onset without morning stiffness. Multiple visceral involvements. No response to corticosteroids	Proteinuria, monoclonal gammopathy or light chain in urine (AL type). Free amyloid debris in synovial fluid; specific birefringence with Congo Red staining on biopsies
Reiter's or psoriatic spondyloarthropathy	Axial, skin, ophthalmic or genitourinary signs and symptoms. Mostly asymmetrical. Occasionally firm and non-pitting lymphoedema	HLA-B27 +; sacroiliitis +
Late onset spondyloarthropathy	Middle aged men. Asymmetrical pitting oedema of lower limbs with oligoarthritis. Constitutional symptoms ++; poor response to corticosteroids	HLA-B27 +; Absent axial disease
Rheumatoid arthritis	Female predominance, symmetrical synovitis of MCPs and IPs. Good (not dramatic) response to corticosteroids. Unilateral pitting oedema, associated with rupture of neighbourhood joint.	RF +, bony erosions on radiography
Polymyalgia rheumatica	Elderly patient with female predominance. True peripheral synovitis – rare; usually mild. Dramatic response to corticosteroids. Long-drawn treatment with frequent flares	Temporal artery biopsy

with concomitant proton-pump inhibitor. The patient took a much longer time (18 months) for complete remission. He used to come regularly for follow-up, and there was no flare up after three years, and his ESR was normal.

Discussion

McCarty *et al*[2] in 1985 first described the RS_3PE syndrome where they studied 10 cases of which 8 were males and 2 females. RS_3PE syndrome, now regarded as a distinct clinical entity, have male preponderance (male:female = 4:1) with affection of mainly the rural or semirural people having involvement of big and small joints of limbs (appendicular joints) associated with tenosynovitis predominantly of flexor tendons of the hands, and accompanied by pitting oedema of dorsum of the hands though oedema of feet/pretibial areas may or may not be present.[2,3] Mean age at presentation in one study was 71 years, with a range of 48 to 86 years, where the onset of symptoms occurred mostly between March to November with a peak in September and October.[3] Another study of 12 cases showed the age ranged between 62 to 85 years. The disease is exquisitely sensitive to small dose of corticosteroids and remission is invariably maintained even after discontinuation of drugs, unlike in RA; predictable complete remission occurs in 3 to 36 months with a mean of 18 months.[3] HLA-B7 association ranges from 50 to 70%.[3,4]

Sudden onset of joint pain in an elderly person obviously resembles PMR; RA remains a possibility at all ages. The marked preponderance in men, a shorter natural course, increased acute phase reactants, the predictable response and remarkable sensitivity to 'low dose prednisolone', complete and sustained remission even after withdrawal of drug, and the frequent presence of HLA-B7 support that RS_3PE syndrome is indeed quite different from both PMR and RA. Drugs used vary widely from NSAIDs, salicylates, hydroxychloroquine, gold salts, and corticosteroids.[1] However, it is noted that in contradiction to McCarty's observation in 1985, most patients fail to respond satisfactorily to NSAIDs.

Though radiologically evident erosions are absent USG seems to be a reliable, easily accessible and cost-effective modality of radiological evaluation of tenosynovitis in RS_3PE syndrome.[5] Nowadays,

researchers are taking advantage of magnetic resonance imaging (MRI) scan to diagnose tenosynovitis.[6]

In fact, the present case studies virtually satisfied all the criteria for definitive diagnosis of the syndrome. To date, in the follow-up, none of these patients has developed definite rheumatic diseases, or malignant diseases, and this is in concordance with observation of other studies.[1,3] Numerous additional cases have since been reported after McCarty described it for the first time. One study from Korea dealt with a man of 72 years also exhibited similar observations as seen in Case 1 of the present series.

Some recent reports focused that RS_3PE syndrome may be part of a paraneoplastic syndrome as it has been reported in association with carcinomas, e.g., gastric carcinoma, endometrial carcinoma, and pancreatic carcinoma; in all cases, complete remission was observed after total resection of the tumour, indicating a true paraneoplastic syndrome.[1] We had no such association in our case series. In the older population, chance occurrence of both diseases may not be excluded, but such examples emphasize the need for a thorough clinical examination in those subset of population. The suspicion of underlying malignant diseases leading to paraneoplastic syndrome should strike the mind of rheumatologists, especially if the response to corticosteroids is poor.[1]

In the clinical setting of RS_3PE syndrome, the rheumatologists should consider the following conditions (Table 1) where arthritis may be associated with pitting oedema of the hands, one of the main characteristics of this syndrome.

The aetiology of RS_3PE syndrome is still unknown. A comparison of clinico-laboratory findings in patients with RS_3PE alone, PMR alone, and RS_3PE associated with PMR has been published by Cantini *et al*.[6] Their results suggest that the three conditions might represent a continuum, with PMR (a more severe condition) at one end and, RS_3PE alone, at the other. PMR (a longer duration disease and is more commonly associated with systemic symptoms) requires higher doses of corticosteroids for a prolonged time, and shows frequent relapses and recurrences. According to Cantini *et al*, the similarities of MRI findings in PMR with distal pitting oedema and pure RS_3PE syndrome seem to indicate that the involvement of extra-articular synovial structures represents the common anatomical target of the inflammatory process in these two conditions. In spite of similarities between PMR and RS_3PE syndrome as emphasized by them, Cantini et al ultimately concluded that RS_3PE alone is a separate entity. Other studies by the same group of authors have shown that RS_3PE may be a feature of different diseases, such as spondyloarthropathies, psoriatic arthritis, RA, sarcoidosis, and neoplasms. According to this study, it is still unknown whether RS_3PE syndrome is a distinct syndrome or a clinical feature of different inflammatory diseases.

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