CASE REPORT

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RS3PE in a Young Female

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Abstract

A 20-year-female presented with acute onset pain and swelling of hands and feet. This was atraumatic and associated with early morning stiffness but not accompanied by rash, Reynaud's phenomenon, fever. Her systemic examination was unremarkable. She was sereonagative for rheumatoid factor, ANA, and her thyroid profile was also normal. Doppler ultrasonography revealed oedema around extensor tendons of hands. She responded dramatically to low-dose steroid. A diagnosis of Remitting Seronegative Symmetrical Synovitis with Pitting Oedema (RS3PE) is made which is very uncommon to find out in young age.

Key words: Remitting seronegative symmetrical synovitis with pitting oedema (RS3PE), rheumatoid arthtritis, polyarthritis.

Introduction

Remitting Seronegative Symmetrical Synovitis with Pitting Oedema (RS3PE), a concept that was first advocated by Mc Carty *et al*[1] in 1938, is a rare syndrome which is a subset of the seronegative symmetric polyarthtitis of older people – predominantly seen in males. It was formerly considered as a subset of rheumatoid arthtritis (RA), but it is now regarded as a distinct disease. We present a case with typical features of RS3PE in a 20-year-old girl.

Case report

A 20-year-female student presented with atraumatic pain and swelling of both hands (involving wrist, metacarpophalangeal and proximal interphalangeal joints) and feet for about three months. This was accompanied with early morning stiffness lasting more than two hours. There were no accompanying features like rash, Raynaud's phenomenon, fever, burning micturition, urethral discharge, or diarrhoea. For the pain and swelling of hands and feet she was prescribed NSAIDs, but with no relief.

Clinical examination revealed marked pitting oedema of the dorsal surface of hands and feet extending up to wrist and ankle (Fig. 1). Swelling was tender but not warm to touch. There was limitation of movements of wrist and MCP joints, and the joints of feet. Her systemic examination was unremarkable.

Laboratory investigations revealed Hb: 11.9 g/dl; TLC: 14,400/mm^3; platelets: 360,000 h/mm^3; ESR: 36 mm in the 1st hour; CRP: > 90 IU/dl. Her LFT, RFT, urine microscopy were normal. Serology was negative for rheumatoid factor, anti CCP, ANA, hepatitis B and C and HIV. Thyroid profile was normal. Ultrasound abdomen and chest X-ray were normal. X-ray of both hands was normal, without any evidence of erosion (Fig. 2). Colour Doppler sonography of small joints of hands revealed extensor tenosynovitis (Fig. 3). CECT chest was normal (done to rule-out a secondary cause such as sarcoidosis or occult malignancy).

A diagnosis of RS3PE was made. The patient was started on oral prednisolone 20 mg/d. She responded extremely well with resolution of swelling and pain within a week and

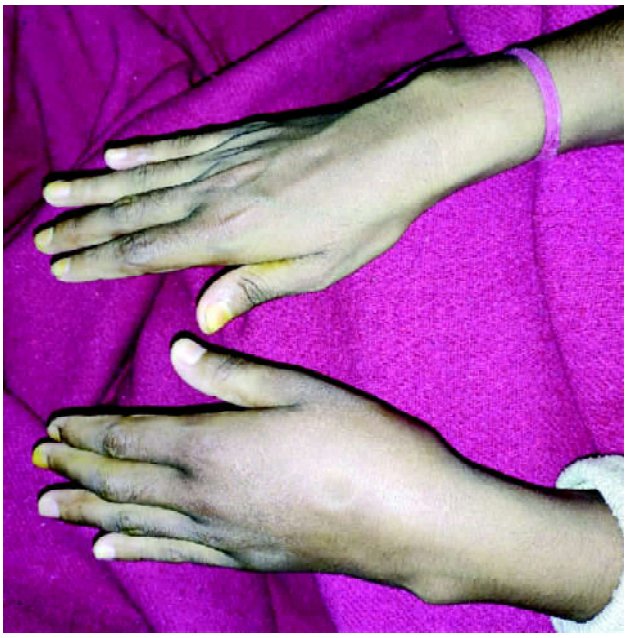

Fig. 1a: *Showing swelling of hands.*

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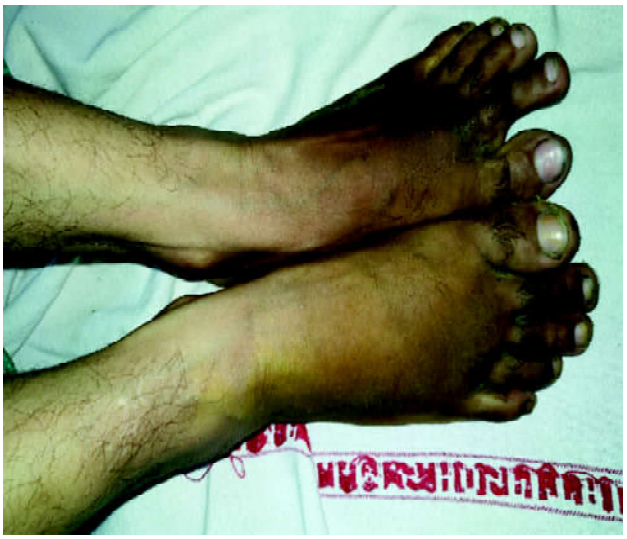

Fig. 1b: *Showing swelling of feet.*

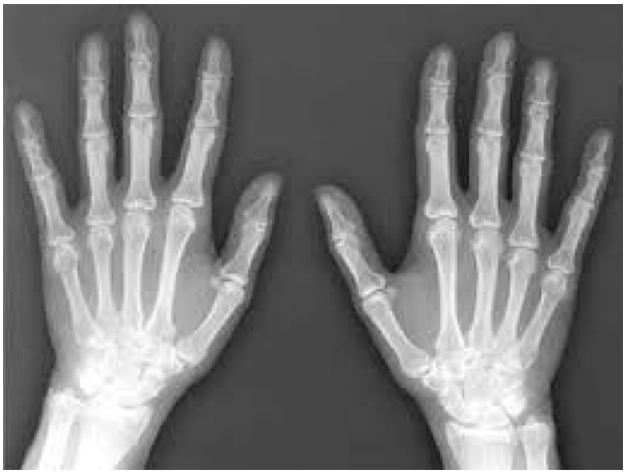

Fig. 2: *Skiagram of both hands AP view.*

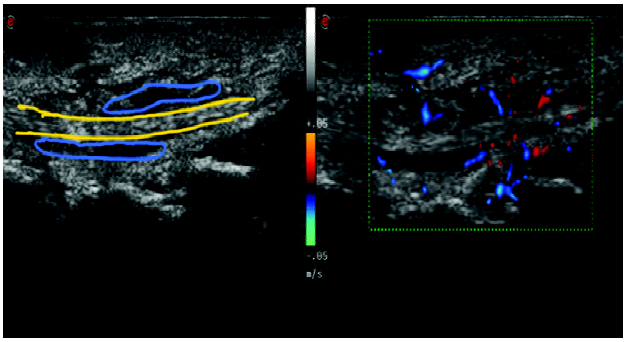

Figure 3a: *Sonographic image on longitudinal view (on the left) depicting fluid (encircled by blue-line) along the extensor digiti minimi tendon (demarcated as two yellow-lines) and also vascularity on colour map (on the right) suggesting active tenosynovitis.*

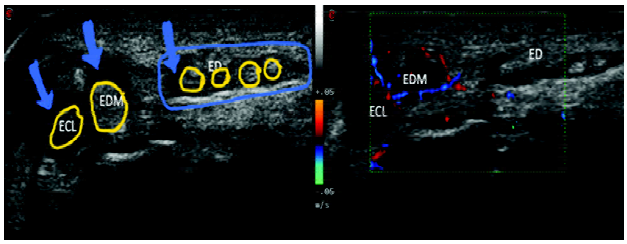

Figure 3b: *Sonographic image on axial section (on the left) showing fluid (blue arrows) and vascularity (on the right) along extensor group of tendons (yellow circles).*

EDM- extensor digiti minimi, ED- extensor digitorum, ECL- extensor carpi ulnaris.

steroid was gradually tapered-off over three months. Till the time of reporting, our patient did not show any sign of relapse.

Discussion

The diagnosis of RS3PE is not easy as it is always hindered by lack of definitive diagnostic criteria and presence of other much common rheumatological diseases that they may mimic. Following a retrospective multicentred study, Olive *et al*[2] proposed the following diagnostic criteria for this syndrome:-

- Bilateral pitting oedema of hands
- Sudden onset of polyarthritis
- Age > 50 years
- Seronegative for Rheumatoid Factor.

Since Mc Carty's original description, over 150 case of RS3PE have been described[3]. Most of them fulfilled the original criteria. However, many cases do not fit the criteria adding new dimensions to this entity. RS3PE has been infrequently reported in young age (< 30 years)[4,5,6].

The association of pitting oedema and arthritis of the hands is very rare. It is very suggestive of RS3PE syndrome. Onset may be rapid, in less than a month. The clinical picture is characterised by a florid pitting oedema of the dorsum of the hands, which may also be present in the feet. Wrist joint movement is often limited and there may be a small effusion in the knee joints. Pain involves the wrists, the MCPs and IPs as well as the flexor tendon sheaths of the fingers. Shoulder girdle pain is also frequently reported, but the pelvic girdle is seldom involved.

Laboratory tests typically demonstrate an inflammatory state with increased erythrocyte sedimentation rate and C-reactive protein, discrete inflammatory anaemia and hypoalbuminaemia. There is seronegativity for rheumatoid factor and ANA, positive for HLA B7. In cases where synovial fluid analyses were carried-out, leucocyte counts were usually lower than in rheumatoid arthritis.

Radiography of the hands and wrists show soft tissue oedema and generalised osteopenia. Bone erosions are absent. MRI studies suggest distinct extensor tenosynovitis as the principle lesion[7].

The immune pathogenesis of RS3PE is still in the dark. The clustering of patients from rural areas and the seasonal variation points towards its infectious or para-infectious origin. Tuberculosis, Parvovirus B19, *Streptobacillus moniliformis*, *E. Coli*, *C. jejuni*, Mycoplasma have all been listed[8]. But causal relationship has not been established. One study has suggested that VEGF as a major contributor to polysynovitis by increasing hypervascularity and vessel permeability, which by turn lead to subcutaneous oedema[9]. IL-6 has been found to be elevated in synovial fluid. Vasculitis of lymphatics has also been postulated[10], but, lymphoscintigraphy studies showed no reduction of axillary lymphnode radioactivity, indicating normal lymphatic function.

There has also been association with HLA B7 and A2 haplotype, however their role in inheritance is still uncertain due to paucity of documented cases. There have been reports of apparently classic RS3PE syndromes that were complicated by connective tissue diseases such as polyarteritis nodosa or other vasculitides. Pitting oedema typical of RS3PE was reported in lupus, ankylosing spondylitis, and temporal arteritis. Patients with seropositive rheumatoid arthtritis can have similar manifestation but bony erosion is invariably present and they relapse after steroid withdrawal.

RS3PE syndrome has also recently emerged as a potential paraneoplastic syndrome. Cases of gastric carcinoma, endometrial carcinoma, and pancreatic carcinoma have been reported. In all cases, complete remission was observed after resection of the tumour, indicating a true paraneoplastic syndrome.

The association of arthritis and oedema of the hands is fairly uncommon and should lead us to consider certain diagnoses when confronted by such cases. RS3PE is not the sole diagnosis.

- Mixed connective tissue disease can present with arthralgia and oedema of hands (including sausaging of digits) with Raynaud's phenomenon (absent in RS3PE).
- Both reactive arthritis and psoriatic arthropathy may present with firm, non-pitting, oedematous hand involvement which is asymmetrical (unike symmetrical involvement in RS3PE).
- Oedema of lower limb with sparing of upper limb has been reported with seronegative spondyloarthropathy.
- Oedema of the hands can be the presentation of reflex sympathetic dystrophy that may be bilateral. Exquisite pain aggravated by active and passive mobilisation, vasomotor and skin alterations, absence of true arthritis, presence of predisposing factors such as myocardial infarction, stroke, or use of barbiturates, and the absence of systemic inflammation, will generally lead to the correct diagnosis.
- Rarely in rheumatoid arthritis, oedema of the hands has been observed during severe flare-ups and hence attributed to changed capillary permeability secondary to the diffuse inflammatory process. Unilateral oedema resulting from a capsular rupture at the wrist, similar to the Baker cyst rupture in the knees, has also been reported. Unlike the prompt response observed in RS3PE, these cases of rheumatoid lymphoedema do not respond well to second-line treatment or corticosteroids. Demonstration of erosions and high leucocyte counts in synovial fluid favours the diagnosis of rheumatoid arthritis.
- Polymyalgia rheumatica is a disease of elderly (like RS3PE) but less likely to present with oedematous extremities – especially upper limbs (unlike RS3PE) – and is prone to recur.

Prognosis is excellent. Duration of treatment is usually less than a year (average 6 - 18 months). Response to NSAID is not good. Low-dose prednisone (10 to 15 mg/day) was found to be effective with a rapid and spectacular effect. RS3PE patients who have underlying malignancy respond poorly to steroid. Surgical removal of tumour – if possible – shows complete remission. Those who poorly respond, hydroxylchloroquine can be added as a disease modifying agent. The literature is silent about the response with other DMARDs in RS3PE. Tocilizumab, a monoclonal antibody against IL-6 receptor, is effective in selected patients with high IL-6 level and can be used in steroid-dependant/ refractory cases. Low-grade flexion contractures may develop on wrists and fingers that may sometimes be permanent.

In the present case, our patient responded to steroid.

Conclusion

RS3PE is an uncommon syndrome but should be considered in a typical clinical scenario as it has an excellent prognosis. The mechanism since understood cannot explain why the elderly are prone to this syndrome. And one must be suspicious of this syndrome in the younger age group too. This case adds clinical aspects to reconsider the 'age' criteria mentioned in the diagnostic criteria as it does not add value to the pathophysiology of the disease, or have any prognostic implications.

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