Remitting Seronegative Symmetrical Synovitis with Pitting Edema (RS<sub>3</sub>PE); A Rare Association with Phyllodes Tumour of Breast


Abstract
Remitting seronegative symmetrical synovitis with pitting edema (RS<sub>3</sub>PE) is a rare entity mainly found in elderly males. It is characterized by pitting edema mainly of dorsum of both hands giving a “boxing glove hand” appearance; rarely involving feet also, acute in onset, negative rheumatoid factor and a good response to low dose corticosteroid therapy. Clinically it almost resembles a case of polymyalgia rheumatica, late onset rheumatoid arthritis or other seronegative spondyloarthropathy. Though there are multiple underlying factors causing this rare entity but it has very close associations with many malignancies. So far its association with solid tumours and hematological malignancies has been reported. Phyllodes tumour of breast shows wide spectrum of activity from a benign condition to a locally aggressive and sometimes metastatic tumour. One fourth of the cases recur after definitive treatment. Our case represent an unusual association with recurrent phyllodes tumour of breast with RS<sub>3</sub>PE.

Introduction
McCarty et al in 1985 reported a series of 10 cases (8 male and 2 female) of a unique syndrome, characterized by acute onset symmetrical synovitis involving the appendicular joints and flexor digitorum tendons. There was pitting edema of the dorsum of hand resembling “boxing glove hand”; as well as edema over feet and pre-tibial region. There may be involvement of other joints like elbow, shoulder, knee and hip joints. He described this distinct subset as “remitting seronegetive symmetrical synovitis with pitting edema (RS<sub>3</sub>PE)”. RS<sub>3</sub>PE is a rare entity found usually in elderly male, aged more than sixty years. Onset of RS<sub>3</sub>PE is usually acute, with bilateral pitting edema of hand and sometimes feet also. Most of the cases meet the American College of Rheumatology (ACR) criteria of rheumatoid arthritis and all are seronegetive for IgM rheumatoid factor. There are no radiological features of rheumatoid arthritis like juxta-articular osteopenia or bony erosions on X-ray of hand and feet. Though there is symptomatic relief with non steroidal anti inflammatory drugs (NSAIDs), the edema of the hand and feet persists. However, there is good response to low dose corticosteroid and hydroxychloroquine. But cases of RS<sub>3</sub>PE which are associated with malignancy have poor response to this conventional treatment, whereas treatment of the underlying malignancy gives good results. We hereby present a case of RS<sub>3</sub>PE associated with Phyllodes tumor of the breast which recurred twice with the relapse of the tumour.

Case Report
A 40 years old Hindu female patient, housewife, married with three children presented with an abrupt onset of fever, malaise, anorexia, painful swelling of hand and feet bilaterally for two weeks. Edema was mainly localized to the dorsum of hand, wrist joint and was pitting in nature (Figure 1). In lower limbs, edema was in dorsum of both feet extending to ankle joint (Figure 2). Joints were non-tender, no redness or local warmth noted. Thorough physical examination revealed a lump in the left breast. General examination revealed only pallor and raised temperature. Examinations of the cardiovascular, pulmonary,
gastrointestinal and genitourinary systems were within normal limit.

Among laboratory investigations, hemoglobin was 9.6 g/dL; erythrocyte sedimentation rate was 74 mm/h, C-reactive protein was 11.4mg/L. Routine urine examination, serum urea, creatinine, lipid profile, liver function test, fasting and postprandial blood sugar were all within normal limit. Throat, stool, blood, urine culture were negative. X-ray of hand and feet revealed soft tissue edema but no erosion. Serum rheumatoid factor, antinuclear antibody, ASO titre, hepatitis-B surface antigen, and anti-HCV antibody were negative. Chest x-ray and computerized tomography scan of thorax revealed no evidence of pleural thickening or effusion and no focal lesion in the lung parenchyma with normal bronchovascular markings. An FNAC from the breast lump suggested Phyllodes tumour. Ultrasonography (USG) with power doppler of hands and feet revealed soft tissue edema in bilateral wrist and ankle joint with increased vascularity in left side, peritendinous collection in both wrist joint, synovial thickening in both wrist and ankle joint. Synovial fluid study from wrist joint showed decreased viscosity, culture of synovial fluid was negative. Serum protein electrophoresis showed normal albumin, increased α1 and β globulin but Ig G, Ig A, Ig M were within normal limit and complement 3 level was increased. A provisional diagnosis of RS,PE was made on the basis of clinical feature and US power doppler study of hand and feet. Patient was put on oral NSAIDs and hydroxychloroquine with considerable improvement in signs and symptoms, but mild edema persisted. Patient was referred to surgical oncologist and breast lump was excised and reconstruction was done with latissimus dorsi flap. Histopathology of the biopsy specimen showed Phyllodes tumour with increased cellularity, mild to moderate pleomorphism, occasional mitosis, no necrosis and the margin of specimen was tumour free (Figure 3). After mastectomy, the pain and swelling of the hand and feet gradually subsided (Figure 4). On routine follow up, patient was symptom free for the next one year.

After one year, the patient again developed progressive painless swelling in the reconstructed area of the left chest wall. There was also swelling of both the hands, associated with pain (Figure 5). CT scan showed a small nodular opacity in the anterior chest wall in left side at the costo-chondral junction. CT guided fine needle aspiration from soft tissue lesion was done and it showed dispersed pleomorphic malignant cell with hyperchromasia and increased nuclear/cytoplasmic ratio, with some spindle shaped cells with bipolar cytoplasm, indicating a recurrence of the Phyllodes tumour. US power doppler study was repeated and revealed soft tissue edema with increased vascularity and peritendinous collection in both wrist joint with synovial thickening in both wrist and ankle joint A diagnosis of recurrence of RS,PE with Phyllodes tumour was made and the patient was given three weekly doses of injection Methyl-prednisolone(80 mg, depo-medrol). There was only mild diminution of musculoskeletal symptoms but the edema persisted. So we referred the case to oncology department where palliative chemotherapy started with Ifosfamide and Adriamycin. After two cycles of chemotherapy under this regimen, edema in hands and feet subsided permanently (Figure 6) and has not recurred till date.

Discussion

Remitting seronegative symmetrical synovitis with pitting
Edema was first described by McCarty et al in 1985 as an acute onset polyarthritis with preponderance to men in the seventh decade of life. It is characterized by acute onset edema involving mainly dorsum of hands, pitting in nature, absence of serum rheumatoid factor and good clinical response to low dose short course of glucocorticoid. After a multicentre study, Olive et al proposed criteria for diagnosis of RS,PE: 1. polyarthritis of sudden onset 2. pitting edema of both hands 3. patient age more than 50 years 4. absence of rheumatoid factor 5. lack of radiographic evidence of joint destruction. Cause of edema is unknown, though in MRI of joint shows that marked extensor tenosynovitis is the main cause of edema affecting subcutaneous and peritendinous soft tissue. In contrast, lymphoscintigraphy studies showed no reduction of axillary lymph node radioactivity, indicating normal lymphatic function. Studies in past showed that it should be called a syndrome not an entity which represents various form of rheumatic disease and neoplastic condition in elderly. It is found to be associated with many solid tumour like carcinoma of stomach, pancreas, colon, endometrium, liver, ovary, prostate etc. and hematological malignancy as a paraneoplastic condition. Cases of RS,PE found associated with malignancy, showed poor response to corticosteroid treatment and have higher frequency of systemic symptoms like fever, anorexia and weight loss. The real cause of such systemic effect is not well understood, but some authors have shown association with increased level of cytokines like interleukin 6, tumour necrosis factor in serum of patients with RS,PE and malignancies. Our case showed a similar association of RS,PE with malignancy. Here the case presented with systemic symptoms like fever, anorexia, later diagnosed as a case with recurrent Phyllodes tumour of breast and finally relieved of the musculoskeletal symptoms by management of the underlying malignancy.

**Conclusion**

As remitting seronegative symmetrical synovitis with pitting edema is found mainly in elderly population and closely associated with various malignancies, physicians must examine every RS,PE case they come across thoroughly, in order to detect some underlying malignancy.

**References**


