Case Report

Bilateral pleural effusion with APLA positivity in a case of rhupus syndrome

Kaushik Saha, Arnab Saha, Mrinmoy Mitra[1], Prabodh Panchadhyayee[2]

Department of Pulmonary Medicine, Burdwan Medical College and Hospital, Burdwan, [1]Calcutta National Medical College, Kolkata, [2]Midnapore Medical College, Midnapur, West Bengal, India

ABSTRACT

Rhupus syndrome is a rare syndrome characterized by overlap of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Our patient was a diagnosed case of RA and developed SLE 2 years after. She was a middle-aged woman, presented with bilateral pleural effusion with exacerbation of skin and joint symptoms of SLE. We diagnosed the case as tubercular pleural effusion by positive *Mycobacterium tuberculosis* in bactec 460 culture. She had also anti-phospholipid antibody positivity without any symptoms and signs of thrombosis.

KEY WORDS: Anti-phospholipid antibody, pleural effusion, rhupus

Address for correspondence: Dr. Kaushik Saha, Rabindra Pally, 1st Lane, Nimta, Kolkata - 700 049, West Bengal, India. E-mail: doctorkaushiksaha@gmail.com

INTRODUCTION

Rhupus syndrome is the combination of clinical and immunological features of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). The patients of this syndrome have features of RA at beginning and few years later the manifestations of SLE develops. It is a very rare clinical entity and still now a very few number of well-documented cases are available in literature. We are reporting a twenty-eight year old young lady of rhupus syndrome with bilateral tubercular pleural effusion and associated positive anti-phospholipid antibody (APLA).

CASE REPORT

A twenty-eight year old married female was diagnosed as rheumatoid arthritis 2 years back based on stiffness, polyarthritis of small joints of both hand, raised rheumatoid arthritis (RA) factor (1:498), positive anti-cyclic citrullinated peptide (anti-CCP) 55 IU; (normal range 0-17 IU). She was on treatment with methotrexate, hydroxychloroquine and episodic analgesics. She had attended our pulmonary medicine outdoor with complaints of dry cough and bilateral pleuritic chest pain with evening rise of temperature for last one month. On enquiry she gave history suggestive of photosensitivity; genital ulcerations; oral mucosal ulcerations; loss of appetite; joint pain with swelling of bilateral small joints of hand and wrist joints and elbows for last three months. She denied any history suggestive of Raynaud's phenomenon, hemoptysis, menstrual irregularities, dysphagia, dryness of mouth and muscle weakness or seizures.

On examination of face, there was presence of mucosal ulcerations in the lower lips with butterfly like rash over malar region [Figure 1]. Joints examination revealed tenderness with swelling of bilateral proximal and distal interphalangeal joints; metacarpophalangeal joints, wrist and elbow joints without any deformity and restriction of movement. There was absence of skin thickening, lymphadenopathy and hepato-splenomegaly but pallor present. Examination of chest revealed bilateral stony dull percussion note over infra-axillary and infra-scapular area with diminished vesicular breath sound suggestive of bilateral pleural effusion. He denied any history of anti-tubercular drug intake, treatment with corticosteroids and contact history of tuberculosis.

Complete blood count was normal except normocytic normochromic anemia with hemoglobin 9.0 gm/dl and raised erythrocyte sedimentation rate 65 mm at

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1st hour. Urine examination showed albuminuria 2+, occasional red blood cells and 24-hour urinary protein as 900 mg/day. Liver function and renal function tests were normal. The X-ray of both hands showed lucency within bilateral triquetral bones and erosion at base of right sided 5th metacarpal bone suggestive of erosive arthritis [Figure 2]. Her chest X-ray postero-anterior view showed bilateral mild pleural effusion [Figure 3]. Her electrocardiography, echocardiography and ultrasonography of whole abdomen were normal. The pleural fluid was straw in colour and its analysis revealed total cell count 750 cells/mm^3 (lymphocytes 95%, and neutrophil 05%), protein 5.1 mg/dl, sugar 64 mg/dl, lactate dehydrogenase 450 U/L and adenosine deaminase 72.9 U/L (normal < 30 U/L). Gram stain, pyogenic culture and Ziehl-Neelsen (Z-N) stain of pleural fluid was negative but bactec 460 culture by ^{14}C-label substrate medium confirmed the presence of *Mycobacterium tuberculosis*. The consecutive 3 days sample of sputum for acid-fast bacilli was negative. On Special investigations, the index value of serum anti-nuclear antibody (ANA) was 6.92 (positive: More than 1.0) with anti- double-stranded DNA (anti-dsDNA) by enzyme immune assay (EIA) 3.73 (cutoff value - 0.52). Serum anti-phospholipid IgG antibody (APLA) by EIA was 2.56 (the cutoff value 0.52) without any symptoms and signs of arterial and venous thrombosis and remains positive on repeat examination after 12 weeks. Serum international normalised ratio (INR) was 0.88. Pleural fluid for lupus erythematosus (LE) cells, ANA and RA factor was negative.

Patient fulfilled 6 out of 11 American College of Rheumatology (ACR) revised criteria for classification of SLE and had a score of 8/10 based on the 2010 American College of Rheumatology/European League against rheumatism classification criteria for RA.[1,2] We had diagnosed the case as bilateral tubercular pleural effusion with APLA positivity in a case of rhupus syndrome and started treatment with daily anti-tubercular therapy consisting of isoniazid 300 mg, rifampicin 450 mg, pyrazinamide 1250 mg and ethambutol 1000 mg and hydroxy-chloroquine (400 mg once daily). Topical hydrocortisone ointment was advised to apply on the oral mucosal and genital ulceration sites thrice daily. Sunscreen lotion containing octinoxate 7.5% w/w, avobenzone 2% w/w, oxybenzone 3% w/w, zinc oxide 2% w/w, with 26 sun-protection factor (SPF) was also advised to apply on the face mainly on the hyper-pigmented spots thrice daily.

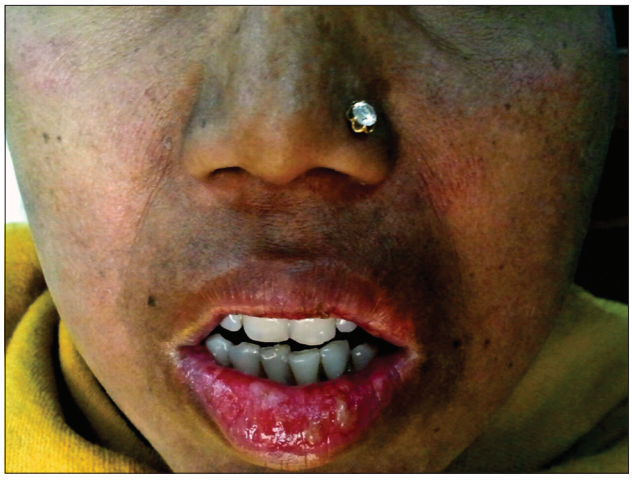

Figure 1: Face examination showing presence of mucosal ulcerations in the lower lips with butterfly like rash over malar region

DISCUSSION

In the year 1974, Schur coined the terminology 'rhupus syndrome' for the first time and he showed the presence of features of both RA as well as SLE.[3] The rhupus syndrome is usually diagnosed by inflammatory symmetrical polyarthritis, raised RA factor, clinical manifestations suggestive of SLE (cutaneous manifestations such as butterfly skin rashes, alopecia, photosensitivity; hematological manifestations such as leucopenia and thrombocytopenia; serositis such as pleural and pericardial effusion and mucosal involvement), positive anti-dsDNA or anti-smith auto antibodies.[4] Amezcua-Guerra LM *et al.*, had used anti-CCP to differentiate RA and rhupus from SLE.[5] The early manifestations of rhupus consist of features of RA and among them the most common presentation is erosive symmetrical polyarthritis followed by rheumatoid nodules (40% cases).[6] Newer imaging modalities like ultrasound (US) with doppler and magnetic resonance imaging (MRI) of joints helps in differentiation of rhupus arthritis from SLE or RA arthritis and detects the severity of joints early with prognostic implications.[7,8] Tani C *et al.*, described differences in the clinical features

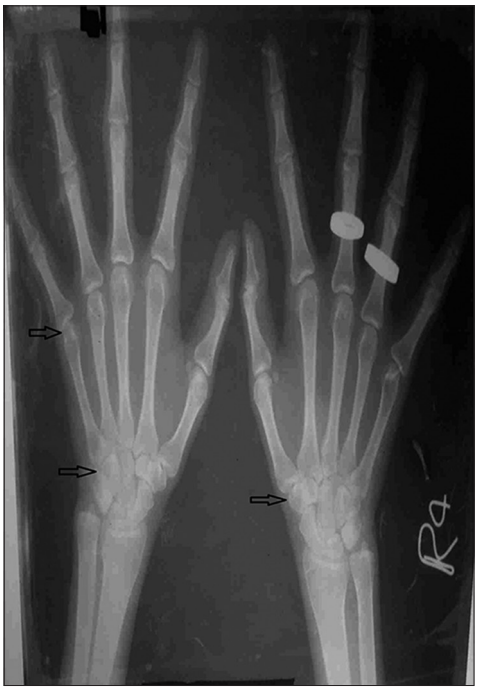

Figure 2: X-ray of both hands showing lucency within bilateral triquetral bones and erosion at base of right sided 5th metacarpal bone suggestive of erosive arthritis (black arrow)

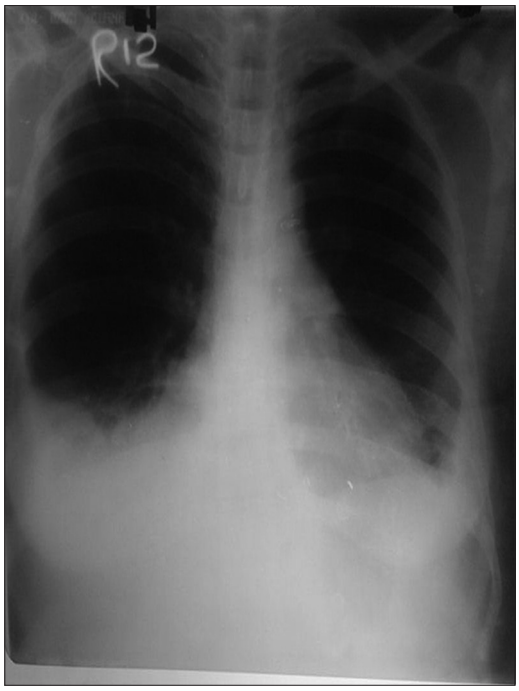

Figure 3: Chest X-ray (postero-anterior view) showing bilateral mild pleural effusion

and joint imaging scores between rhupus patients and SLE patients.[8] In this study at least one pathological finding (synovitis or bone erosion) was observed by US examination of hand or wrist joints in all rhupus patients and statistically significant higher scores on US was detected in respect to SLE patients but RA patients had similar scores. MRI of joints also showed the similar findings like US.[8] Rhupus patients had significantly lesser involvement of kidney compared with SLE patients, but no differences were observed regarding the involvement of hematological, serositis, neuropsychiatric and cutaneous by Tani C *et al*.[8] The features of SLE develop several years after the onset of the features of RA probably due to precipitation of some hormonal factors.[9] We diagnosed our case as rhupus syndrome by the clinical features of RA and SLE with erosive arthritis, positive RA, Anti-CCP, ANA and Anti-dsDNA. In our patient manifestations of SLE appeared two years after the diagnosis of RA made. In rhupus syndrome extra-articular major organ involvement is extremely unusual though lupus encephalitis and lupus pnemonitis were reported.[4,10] These patients have APLA positivity in high titers but symptomatic thrombosis is very rare.[11]

Pleural effusion in a patient of rhupus syndrome can occur due to different reasons like rheumatoid pleuritis, lupus pleuritis, parapneumonic, tuberculosis etc., Predominant cell type in parapneumonic effusion is neutrophilic but in other causes (rheumatoid, lupus and tubercular) of effusions is lymphocytic mostly. Patients with lupus pleuritis have higher pleural fluid pH (>7.35), higher pleural fluid glucose levels (>60 mg/dl), and lower pleural fluid LDH levels (<500 IU/L or < 2 times the upper limit of normal for serum) than patients with rheumatoid pleuritis and tubercular effusion.[12] There are no available reports still yet of association of tubercular pleural effusion in a case of rhupus syndrome. The confirmatory diagnosis of tubercular pleural effusion is very difficult because of presence of very low number of bacilli in pleural fluid. The overall diagnostic sensitivity of acid-fast bacilli smear by Z-N staining is only 17.5% and Bactec culture is 45% in a recent study.[13] The Bactec 460 TB system is very much superior to Lowenstein-Jensen (LJ) medium for detection of Mycobacteria especially for extrapulmonary tuberculosis.[14] In our case tubercular pleural effusion was diagnosed by Bactec 460 culture. However, we would like to highlight the necessity of Bactec 460 culture in a case of pleural effusion in rhupus.

Treatment of arthritis in rhupus patients mainly involves symptomatic treatment with non-steroidal anti-inflammatory drugs in case of occasional arthralgia and disease modifying rheumatic drugs like hydroxyl chloroquine or methotrexate in case of persistent arthritis. In refractory rhupus patients, rituximab is a safe and effective therapeutic option.[15]

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