ejpmr, 2020,7(12), 110-113

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

RHUPUS: 5 CASES-BASED LITERATURE REVIEW

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Article Received on 08/10/2020 **Article Revised on 28/10/2020** **Article Accepted on 18/11/2020**

ABSTRACT

Introduction: Rhupus is a rare entity that combines systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). The aim of this study is to describe the clinical and immunological profile of this disease. **Materials and methods:** Descriptive study of 5 patients with rhupus and follow-up by an internal medicine department over a period from 2005 to 2020. Diagnosis selected according to the ACR criteria of PR and SLIIC of LES. **Result:** These were 4 women and a man of an average age at diagnosis 51.8 years [43-58 years]. The mean duration of follow-up was 16.4 years. RA was initiator in three patients and two cases started with rhupus. Rhupus was associated with Gougerot Sjogren syndrome (n=3); anti-phospoholipid syndrome (n=2); primary biliary chirrosis (n=1) and leukocytoclastic vasculitis (n=1). Polyarthralgia was present in all of our patients; photosensitivity and malar rash in 2 patients. Two patients had Raynaud syndrm and arthritis. Hemolytic anemia with a positive CDT was noted in 2 patients. Hypergammaglobulinemia was noted in 3 patients. All of our patients had positive RF, anti CCP and ANA with titers ranged from 1/400 to 1/12,800. Three of our patients had positive anti native DNA. Two patients presented positif aCL and / or ACC and / or anti b2GPI. Anti-SSA were positif in 2 cases anti SSB (n =1) anti histone: (n =1) anti Sm (n=1) and anti RNP (n = 2). All of our patients were put on corticosteroid therapy and methotrexate and hydroxychloroquine was prescribed in 2 patients. **Conclusion:** Rhupus mainly concerns young women in the third decade. The clinical manifestations are essentially cutaneous articular.

KEYWORDS: Rheumatoid arthritis, overlap, systemic Lupus Erythematosus.

INTRODUCTION

Rhupus represents an overlap of Systemic Lupus Erythematosus (SLE) and Rheumatoid Artiritis (RA). This rare and incompletely understood pathology has no validated classification criteria. And the real burden of rhupus remains unknown.[1] Herein, we present a series of cases that analyze clinical and serologic characteristics of patients with a diagnosis of rhupus.

OBJECTIVE AND METHODS

The aims of this case-based review were:
to report 5 new cases of Rhupus syndrome, classified according the Systemic Lupus International Collaborating Clinics (SLICC) 2012 criteria for SLE and the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2010 criteria for RA, and to perform a systematic review of similar case reports (patients with TA and SpA or TA occurring under anti-TNF). The authors performed a systematic search of case reports or case series of patients with rhupus syndrome in PubMed, Scopus and google scholar from the onset until October 2020 and using the following combination of words: “rhupus” “lupus AND rheumatoid arthritis AND overlap” .The language was restricted to English. The discussion was based on the case study and a literature review.

RESULTS

Table 1: Demographic, clinical and immunological characteristics of rhupus’ patients.

	Case 1	Case 2	Case 3	Case 4	Case 5
Age	53	52	43	58	53
Gender	F	M	F	F	F
First diagnosis	RA	RA and SLE	RA	RA	RA and LES
Time since onset, years	31	2	10	15	11
Clinical manifestation	photosensitivity Morning stiffness Erosive arthritis Hemolytic anemia	Sicca syndrome Raynaud Cutaneous Vasculitis	Photosensitivity Alopecia Hemolytic anemia Leukopenia Lymphopenia	Photosensitivity Butterfly blush Erosive arthritis interstitial nephritis	Butterfly blush Morning stiffness Tetrapyramidal syndrome Telangiectasia

	Leukopenia Lymphopenia rheumatoid nodule	Leukopenia lymphopenia		swan neck deformity synovitis	carpal tunnel syndrome
Laboratory examination	HGG Low complement BIS	HGG DCT (+) (IgG) BIS	HGG DCT (+) Low complement BIS	Low complement BIS	BIS
Immunological features	AAN 1/3200 DNA (+) FR (+) Anti CCP (+) Anti RNP (+) Anti-Nucleosome (+)	AAN 1/3200 DNA (+) Anti CCP (+) FR (+) Ro52-SSA (+) SSB (+) pANCA (+) anti-Histone (+)	AAN 1/400 Anti DNA 1/558 FR (+) Anti CCP (+) Ro52-SSA (+) Anti-nuclesome (+) Anti-mitochondrial (+) anti GP 210 ANTi SP100 (+) Anti PML (+) aCL (+) ACC (+)	AAN 1/12800 DNA 1/800 FR (+) anti CCP (+) RNP(+) pANCA (+)	AAN 1/400 DNA (+) FR (+) anti CCP (+) Anti-Sm (+) ACC (+) b2GPI (+)
SLICC criteria	6	4	8	6	7
RA ACR criteria	7	6	6	7	6
Association	SS	SS, pANCA	SAPL, PBC, SS	SS	SAPL
Treatment	CT, MTX, HCQ	CT, MTX, HCQ	CT, HCQ, ursolvan	CT, MTX, HCQ	CT, MTX, HCQ
Response to DMARD treatment	Good	Lost to follow up	*Digestive intolerance to MTX *3 exacerbations of RA	Good	Good

- *HGG: hypergammaglobulinemia
- **DCT: direct coombs test
- BIS: biological inflammatory syndrome
- SS: sjogren syndrome
- PBC: Primary biliary cirrhosis
- CT: corticotherapy
- MTX: methotrexate
- HCQ: hydroxychloroquine

Demographic, clinical and immunological characteristics of the five patients studied are seen in Table 1. Two of our patients presented symmetric chronic bilateral and erosive polyarthritis, one of them with subcutaneous nodules. Three patients presented an initial diagnosis of RA and two patients had concomitant SLE and RA.

Three patients had 6 classification criteria for RA and two had 7. All the patients had 4 or more criteria for SLE. All our patients were treated with combined therapy with corticosteroid, hydroxychloroquine and methotrexate with a clinical remission achievement in the majority of them.

DISCUSSION

The coexistence of SEL and RA is rare and estimated between 0.01% and 2%.[1] The definition of rhupus syndrome remains controversial and challenging, despite the increasing number of authors reporting patients with both SLE and RA features.

Several combinations of clinical, biological and radiological criteria have been used in the literature, but no one has been validated.

Generally, RA characteristics dominate the clinical picture, with erosive symmetric polyarthritis in 40% of these patients.[3] The most common SLE characteristics in rhupus are usually hematological (leukopenia, thrombocytopenia), skin and mucosal involvement and serositis (pleural and pericardial effusion).[3] Lupus' skin manifestations have low incidence in rhupus.

Rhupus arthropathy has generally a clinical and radiological RA-like distribution, and no significant differences are found in the frequencies of morning stiffness, joint pain and symmetrical polyarthritis when compared to RA.[4]

Studies showed that the most affected joints are radiocarpal and intercarpal joints for the wrist and proximal interphalangeal joints or metacarpophalangeal joints for the hand.[5,6]

Patients with erosions have higher titers of anti-CCP antibodies when compared to SLE patients with nonerosive arthritis.[7]

When compared to SLE patients.[5,6,8] rhupus patients have lower SLEDAI scores with less frequent and less severe systemic involvement such as neurological

involvement, malar rash, renal and hematological abnormalities.

But, when compared to SLE patients, rhupus patients have a similar prevalence of positive antinuclear (ANAs), anti-dsDNA and anti-Sm antibodies,[5,6]

Two of the five patients with rhupus had positive anti-CCP. The presence of elevated anti-CCP antibodies are highly specific (96%–98%) in patients with RA.[10] Patient with anti-citrullinated antibodies are more likely to have erosive arthritis.[9,10]

Rhupus patients and SLE patients with erosive arthritis of all kinds are more likely to have CRP and ESR more increased than in patients with nonerosive SLE[8,6]

Two of our patients presented antiphospholipid antibodies but none presented clinical manifestations of antiphospholipid syndrome. Which have been also reported in other cases.[3,2]

All our patients had Sjogren' syndrome and rhupus was associated to vasculitis in two cases with positive pANCA. The associations between rhupus and other autoimmune diseases are not well understood, but overlaps with autoimmune hepatitis,[11] polyarteritis nodosa,[12] inflammatory myositis[13] and autoimmune thyroiditis[14] have been reported.

The long-term natural history of the disease is not well described. SLEDAI, SLEDAI-2K and DAS28 have been applied to rhupus in many reported studies[8,15,16] even DAS28 score has been proposed to evaluate the articular involvement in SLE patients[17]

Despite the growing number of case reports and series on rhupus, validated classification criteria do not exist. Thus, Physicians should remain alert to manifestations of autoimmunity and overlapping disease features in order to recognize and prompt diagnosis for an effective treatment of this disease. Large prospective studies evaluating patients from the first symptoms through a long follow-up period are necessary in order characterize its clinical and immunologic phenotype.

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